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NCBI *results of* BLAST

BLASTP 2.2.9 [May-01-2004]

Reference:
Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schäffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402.

RID: 1091205055-3465-104253815593.BLASTQ4

Query=
(340 letters)

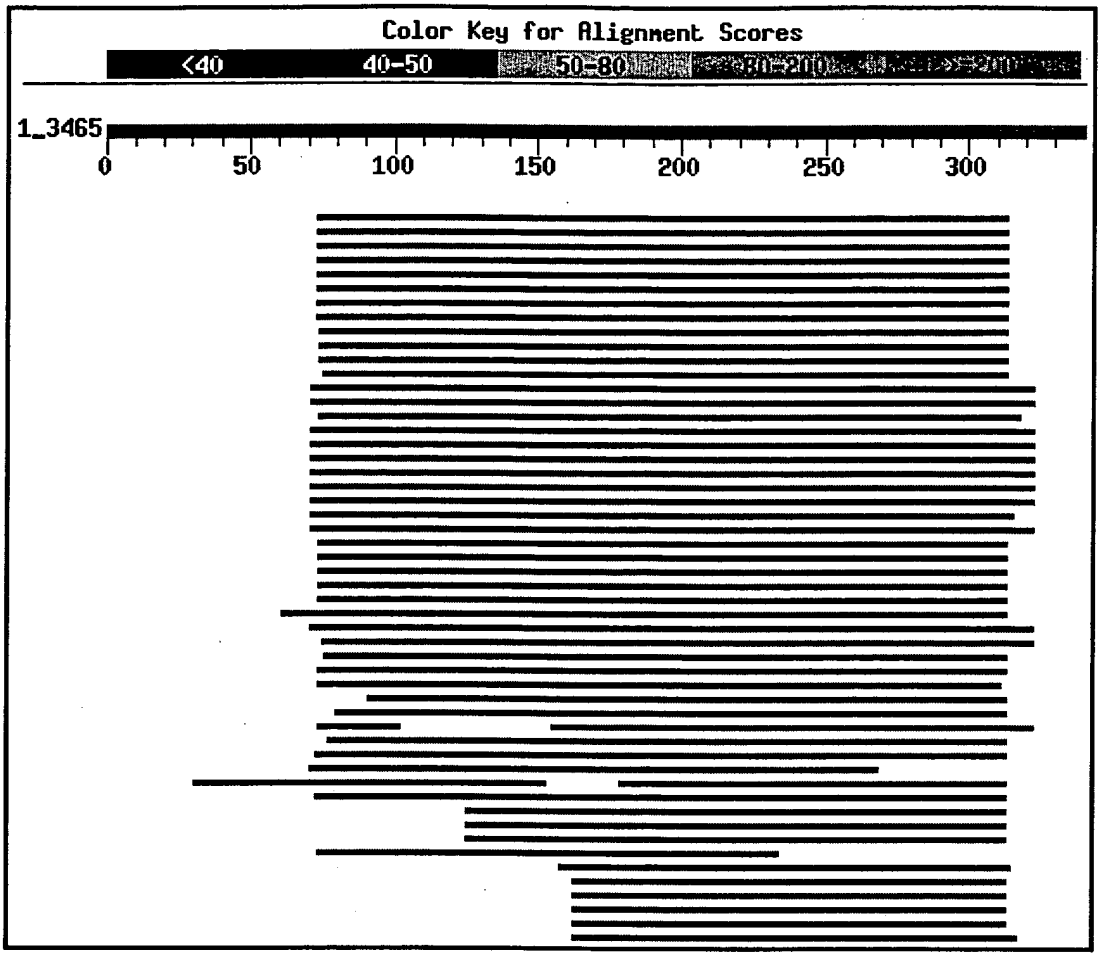
Database: All non-redundant GenBank CDS translations+PDB+SwissProt+PIR+PRF excluding environmental samples
1,958,132 sequences; 658,882,765 total letters

If you have any problems or questions with the results of this search please refer to the **BLAST FAQs**

Taxonomy reports

Distribution of 105 Blast Hits on the Query Sequence

Mouse-over to show defline and scores. Click to show alignments



Sequences producing significant alignments:	Score (bits)	E Value	
gi|15128561|dbj|BAB62751.1| dermatomyositis associated with...	785	0.0	L
gi|19263664|gb|AAH25264.1| YTHDF1 protein [Homo sapiens]	785	0.0	L
gi|31377750|ref|NP_060268.2| YTH domain family 1; chromosom...	785	0.0	L
gi|13277546|gb|AAH03681.1| YTHDF1 protein [Homo sapiens]	785	0.0	L
gi|34782977|gb|AAH16920.2| YTHDF1 protein [Homo sapiens]	785	0.0	L
gi|21740024|emb|CAD39029.1| hypothetical protein [Homo sapi...	785	0.0	L
gi|30424609|ref|NP_776122.1| YTH domain family 1 [Mus muscu...	725	0.0	L
gi|34861007|ref|XP_215979.2| similar to Dermatomyositis ass...	721	0.0	L
gi|50758777|ref|XP_417412.1| PREDICTED: similar to Dermatom...	711	0.0	
gi|45361633|ref|NP_989392.1| hypothetical protein MGC75606 ...	645	0.0	L
gi|38014398|gb|AAH60445.1| MGC68505 protein [Xenopus laevis]	639	0.0	L
gi|47086617|ref|NP_997878.1| similar to RIKEN cDNA 2210410K...	600	e-170	L
gi|40255135|ref|NP_689971.2| YTH domain family 3 [Homo sapi...	571	e-161	L
gi|50738020|ref|XP_419227.1| PREDICTED: similar to High glu...	571	e-161	
gi|7705411|ref|NP_057342.1| high glucose-regulated protein ...	570	e-161	L
gi|21751834|dbj|BAC04046.1| unnamed protein product [Homo s...	568	e-160	L
gi|44890479|gb|AAH67040.1| Ythdf3 protein [Mus musculus]	568	e-160	L

gi|26347625|dbj|BAC37461.1|	unnamed protein product [Mus mu...	568	e-160 L
gi|30962830|gb|AAH52631.1|	Ythdf3 protein [Mus musculus]	568	e-160 L
gi|26343683|dbj|BAC35498.1|	unnamed protein product [Mus mu...	568	e-160 L
gi|46048312|ref|NP_766265.2|	YTH domain family 3 [Mus muscu...	568	e-160 L
gi|34855501|ref|XP_342218.1|	similar to hypothetical protei...	568	e-160 L
gi|26333099|dbj|BAC30267.1|	unnamed protein product [Mus mu...	566	e-160 L
gi|41019527|sp|Q9Y5A9|HGR8_HUMAN	High-glucose-regulated pro...	563	e-159 L
gi|19851923|gb|AAL99921.1|	CLL-associated antigen KW-14 [Ho...	563	e-159 L
gi|20809771|gb|AAH28994.1|	High glucose-regulated protein 8...	563	e-159 L
gi|15928654|gb|AAH14797.1|	High glucose-regulated protein 8...	563	e-159 L
gi|30841028|ref|NP_663368.2|	high glucose-regulated protein...	563	e-159 L
gi|50759678|ref|XP_417730.1|	PREDICTED: similar to High-glu...	559	e-158
gi|21732274|emb|CAD38530.1|	hypothetical protein [Homo sapi...	557	e-157 L
gi|41054079|ref|NP_956164.1|	Similar to RIKEN cDNA 9130022A...	544	e-153 L
gi|47223342|emb|CAG04203.1|	unnamed protein product [Tetrao...	534	e-150
gi|41053800|ref|NP_956544.1|	hypothetical protein MGC56224 ...	533	e-150 L
gi|38086386|ref|XP_205340.3|	similar to High glucose-regula...	514	e-144 L
gi|50418347|gb|AAH78013.1|	Unknown (protein for MGC:82537) ...	491	e-137
gi|46329541|gb|AAH68959.1|	MGC83235 protein [Xenopus laevis]	488	e-136 L
gi|18605766|gb|AAH22932.1|	Ythdf3 protein [Mus musculus]	466	e-130 L
gi|47230021|emb|CAG10435.1|	unnamed protein product [Tetrao...	462	e-129
gi|47229164|emb|CAG03916.1|	unnamed protein product [Tetrao...	440	e-122
gi|16551561|dbj|BAB71122.1|	unnamed protein product [Homo s...	432	e-119 L
gi|47207024|emb|CAF91623.1|	unnamed protein product [Tetrao...	409	e-112
gi|24649883|ref|NP_733067.1|	CG6422-PB [Drosophila melanoga...	348	2e-94 L
gi|21356147|ref|NP_651322.1|	CG6422-PA [Drosophila melanoga...	348	2e-94 L
gi|31202859|ref|XP_310378.1|	ENSANGP00000005606 [Anopheles ...	348	2e-94
gi|25012679|gb|AAN71434.1|	RE55836p [Drosophila melanogaster]	348	2e-94
gi|34871864|ref|XP_232772.2|	similar to High-glucose-regula...	317	7e-85 L
gi|42407463|dbj|BAD10396.1|	putative rubisco subunit bindin...	258	2e-67
gi|7020460|dbj|BAA91138.1|	unnamed protein product [Homo sa...	257	7e-67 L
gi|30682438|ref|NP_187912.2|	expressed protein [Arabidopsis...	254	5e-66
gi|15795138|dbj|BAB02516.1|	unnamed protein product [Arabid...	254	5e-66
gi|7487895|pir||T01030	hypothetical protein YUP8H12R.13 - A...	250	1e-64
gi|18412316|ref|NP_565205.1|	expressed protein [Arabidopsis...	250	1e-64
gi|38636667|dbj|BAD02987.1|	putative Rubisco subunit bindin...	244	3e-63
gi|42562361|ref|NP_174117.2|	expressed protein [Arabidopsis...	243	8e-63
gi|25403046|pir||A86405	unknown protein [imported] - Arabid...	243	8e-63
gi|22773231|gb|AAN06837.1|	Putative RNA-binding protein [Or...	239	1e-61
gi|49072100|ref|XP_400339.1|	hypothetical protein UM02724.1...	237	5e-61
gi|34911170|ref|NP_916932.1|	B1144G04.32 [Oryza sativa (jap...	237	7e-61
gi|15912287|gb|AAL08277.1|	AT5g61020/maf19_20 [Arabidopsis ...	233	7e-60
gi|30697466|ref|NP_568932.2|	YT521-B-like family protein [A...	233	7e-60
gi|18087662|gb|AAL58954.1|	putative RNA-binding protein [Or...	233	7e-60
gi|30697464|ref|NP_851236.1|	YT521-B-like family protein [A...	233	7e-60
gi|30682683|ref|NP_850578.1|	expressed protein [Arabidopsis...	231	3e-59
gi|30682679|ref|NP_187955.2|	expressed protein [Arabidopsis...	231	3e-59
gi|25084169|gb|AAN72190.1|	Unknown protein [Arabidopsis tha...	231	3e-59
gi|38567895|emb|CAE03650.2|	OSJNBa0060N03.15 [Oryza sativa ...	230	7e-59
gi|50256866|gb|EAL19584.1|	hypothetical protein CNBG2130 [C...	228	2e-58
gi|42573716|ref|NP_974954.1|	expressed protein [Arabidopsis...	226	1e-57
gi|22327938|ref|NP_200627.2|	expressed protein [Arabidopsis...	226	1e-57
gi|8777320|dbj|BAA96910.1|	unnamed protein product [Arabido...	226	1e-57

gi|30682433|ref|NP_850572.1| expressed protein [Arabidopsis...	226	1e-57	
gi|18405397|ref|NP_564692.1| expressed protein [Arabidopsis...	225	2e-57	
gi|25372787|pir||C96597 Rubisco subunit binding-protein bet...	225	2e-57	
gi|15221079|ref|NP_175245.1| expressed protein [Arabidopsis...	225	3e-57	
gi|50509741|dbj|BAD31793.1| high-glucose-regulated protein ...	218	4e-55	
gi|30684473|ref|NP_188359.2| expressed protein [Arabidopsis...	216	2e-54	
gi|11994550|dbj|BAB02737.1| unnamed protein product [Arabid...	216	2e-54	
gi|8778514|gb|AAF79522.1| F21D18.17 [Arabidopsis thaliana]	215	2e-54	
gi|30678991|ref|NP_850510.1| expressed protein [Arabidopsis...	203	8e-51	
gi|18396717|ref|NP_566218.1| expressed protein [Arabidopsis...	203	8e-51	
gi|6223640|gb|AAF05854.1| unknown protein [Arabidopsis thal...	203	8e-51	
gi|29725575|gb|AAO89229.1| putative RNA-binding protein [Av...	190	7e-47	
gi|46359911|gb|AAS88843.1| unknown protein [Oryza sativa (j...	186	1e-45	
gi|34894834|ref|NP_908742.1| P0554D10.20 [Oryza sativa (jap...	182	3e-44	
gi|15887004|dbj|BAB69445.1| hypothetical protein [Oryza sat...	182	3e-44	
gi|38346520|emb|CAE03815.2| OSJNBa0027H09.15 [Oryza sativa ...	177	5e-43	
gi|30681366|ref|NP_172452.2| expressed protein [Arabidopsis...	173	1e-41	
gi|25402579|pir||C86232 hypothetical protein [imported] - A...	162	2e-38	
gi|46437279|gb|EAK96628.1| hypothetical protein CaO19.9494 ...	155	2e-36	
gi|50422773|ref|XP_459963.1| unnamed protein product [Debar...	143	1e-32	
gi|6320582|ref|NP_010662.1| Hypothetical ORF; Ydr374cp [Sac...	100	2e-19	
gi|50284935|ref|XP_444895.1| unnamed protein product [Candi...	95	4e-18	
gi|45185527|ref|NP_983243.1| ACL161Cp [Eremothecium gossypi...	83	3e-14	
gi|50308115|ref|XP_454058.1| unnamed protein product [Kluyv...	66	2e-09	
gi|42572881|ref|NP_974537.1| YT521-B-like family protein [A...	65	6e-09	
gi|42566517|ref|NP_192934.2| YT521-B-like family protein [A...	65	6e-09	
gi|16805187|ref|NP_473215.1| conserved protein, putative; r...	63	1e-08	
gi|26351303|dbj|BAC39288.1| unnamed protein product [Mus mu...	62	5e-08	L
gi|23484345|gb|EAA19708.1| hypothetical protein [Plasmodium...	56	3e-06	
gi|16128857|ref|NP_415410.1| cell division protein; cell di...	43	0.020	

Alignments

Get selected sequences | Select all | Deselect all

☐ >gi|15128561|dbj|BAB62751.1| L dermatomyositis associated with cancer putative autoantigen-1
sapiens]
Length = 437

Score = 785 bits (1844), Expect = 0.0
Identities = 242/242 (100%), Positives = 242/242 (100%)

```
Query: 74  AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 133
           AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS
Sbjct: 180 AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 239

Query: 134 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 193
           VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL
Sbjct: 240 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 299

Query: 194 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 253
           DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV
Sbjct: 300 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 359

Query: 254 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 313
           KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK
```

```
Sbjct: 360 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 419

Query: 314 RQ 315
           RQ
Sbjct: 420 RQ 421
```

☐ >gi|19263664|gb|AAH25264.1| L YTHDF1 protein [Homo sapiens]
Length = 502

```
 Score =  785 bits (1844), Expect = 0.0
 Identities = 242/242 (100%), Positives = 242/242 (100%)

Query: 74  AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 133
           AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS
Sbjct: 245 AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 304

Query: 134 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 193
           VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL
Sbjct: 305 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 364

Query: 194 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 253
           DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV
Sbjct: 365 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 424

Query: 254 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 313
           KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK
Sbjct: 425 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 484

Query: 314 RQ 315
           RQ
Sbjct: 485 RQ 486
```

☐ >gi|31377750|ref|NP_060268.2| L YTH domain family 1; chromosome 20 open reading frame 21 [Hc
sapiens]
gi|28380041|sp|Q9BYJ9|DACA_HUMAN L Dermatomyositis associated with cancer putative autoantige
(DACA-1)
gi|12711367|emb|CAC09391.3| L dJ963E22.1 (Novel protein similar to NY-REN-2 Antigen) [Homo
sapiens]
gi|29791407|gb|AAH50284.1| L YTH domain family 1 [Homo sapiens]
Length = 559

```
 Score =  785 bits (1844), Expect = 0.0
 Identities = 242/242 (100%), Positives = 242/242 (100%)

Query: 74  AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 133
           AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS
Sbjct: 302 AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 361

Query: 134 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 193
           VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL
Sbjct: 362 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 421

Query: 194 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 253
           DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV
```

```
Sbjct: 422 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 481

Query: 254 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 313
           KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK
Sbjct: 482 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 541

Query: 314 RQ 315
           RQ
Sbjct: 542 RQ 543
```

☐ >gi|13277546|gb|AAH03681.1| YTHDF1 protein [Homo sapiens]
Length = 548

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 Score =  785 bits (1844), Expect = 0.0
 Identities = 242/242 (100%), Positives = 242/242 (100%)

Query: 74  AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 133
           AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS
Sbjct: 291 AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 350

Query: 134 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 193
           VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL
Sbjct: 351 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 410

Query: 194 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 253
           DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV
Sbjct: 411 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 470

Query: 254 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 313
           KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK
Sbjct: 471 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 530

Query: 314 RQ 315
           RQ
Sbjct: 531 RQ 532
```

☐ >gi|34782977|gb|AAH16920.2| YTHDF1 protein [Homo sapiens]
Length = 462

```
 Score =  785 bits (1844), Expect = 0.0
 Identities = 242/242 (100%), Positives = 242/242 (100%)

Query: 74  AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 133
           AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS
Sbjct: 205 AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 264

Query: 134 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 193
           VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL
Sbjct: 265 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 324

Query: 194 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 253
           DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV
Sbjct: 325 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 384

Query: 254 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 313
```

```
            KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK
Sbjct: 385 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 444

Query: 314 RQ 315
            RQ
Sbjct: 445 RQ 446
```

☐ >gi|21740024|emb|CAD39029.1| L hypothetical protein [Homo sapiens]
Length = 364

```
 Score =  785 bits (1844), Expect = 0.0
 Identities = 242/242 (100%), Positives = 242/242 (100%)

Query: 74  AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 133
            AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS
Sbjct: 107 AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 166

Query: 134 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 193
            VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL
Sbjct: 167 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 226

Query: 194 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 253
            DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV
Sbjct: 227 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 286

Query: 254 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 313
            KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK
Sbjct: 287 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 346

Query: 314 RQ 315
            RQ
Sbjct: 347 RQ 348
```

☐ >gi|30424609|ref|NP_776122.1| L YTH domain family 1 [Mus musculus]
gi|28380032|sp|P59326|DACA_MOUSE L Dermatomyositis associated with cancer putative autoantige
homolog (DACA-1 homolog)
gi|26338351|dbj|BAC32861.1| L unnamed protein product [Mus musculus]
gi|38181496|gb|AAH61479.1| L Ythdf1 protein [Mus musculus]
gi|40674799|gb|AAH65050.1| L YTH domain family 1 [Mus musculus]
Length = 559

```
 Score =  725 bits (1702), Expect = 0.0
 Identities = 227/242 (93%), Positives = 231/242 (95%)

Query: 74  AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 133
            AQPLP QPP L QPQYQSPQQP Q RWVAPRNRNAAFGQSGGA SDSNS GN QP SAPS
Sbjct: 302 AQPLPVQPPPLVQPQYQSPQQPLQPRWVAPRNRNAAFGQSGGANSDSNSVGNAQPTSAPS 361

Query: 134 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 193
            VESHPVLEKLKAAHSYNPKEF+WNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL
Sbjct: 362 VESHPVLEKLKAAHSYNPKEFDWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 421

Query: 194 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 253
            D AFR MSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDV+WIFV
```

```
Sbjct: 422 DGAFRSMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVKWIFV 481

Query: 254 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 313
           KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII+SYKHTTSIFDDF+HYEK
Sbjct: 482 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIASYKHTTSIFDDFSHYEK 541

Query: 314 RQ 315
           RQ
Sbjct: 542 RQ 543
```

☐ >gi|34861007|ref|XP_215979.2| similar to Dermatomyositis associated with cancer putative autoantigen-1 homolog (DACA-1 homolog) [Rattus norvegicus]
Length = 638

```
 Score =  721 bits (1694), Expect = 0.0
 Identities = 226/242 (93%), Positives = 231/242 (95%)

Query: 74  AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 133
           AQPLP QPP L QPQYQSPQQP Q RWVAPRNRNAAFGQSGGA SDSNS G+ QP SAPS
Sbjct: 381 AQPLPVQPPPLVQPQYQSPQQPLQPRWVAPRNRNAAFGQSGGANSDSNSVGSAQPTSAPS 440

Query: 134 VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 193
           VESHPVLEKLKAAHSYNPKEF+WNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL
Sbjct: 441 VESHPVLEKLKAAHSYNPKEFDWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRL 500

Query: 194 DSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFV 253
           D AFR MSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDV+WIFV
Sbjct: 501 DGAFRSMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVKWIFV 560

Query: 254 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEK 313
           KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII+SYKHTTSIFDDF+HYEK
Sbjct: 561 KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIASYKHTTSIFDDFSHYEK 620

Query: 314 RQ 315
           RQ
Sbjct: 621 RQ 622
```

☐ >gi|50758777|ref|XP_417412.1| PREDICTED: similar to Dermatomyositis associated with cancer putative autoantigen-1 homolog (DACA-1 homolog) [Gallus gallus]
Length = 834

```
 Score =  711 bits (1671), Expect = 0.0
 Identities = 220/241 (91%), Positives = 231/241 (95%)

Query: 75  QPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPSV 134
           QP+PAQPP L QPQYQSPQQPPQ RW+APRNRNAAFGQSGG G+DSNS G+ QPN  PS
Sbjct: 305 QPVPAQPPPLTQPQYQSPQQPPQNRWIAPRNRNAAFGQSGGTGNDSNSAGSTQPNPVPSG 364

Query: 135 ESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLD 194
           ESHPVLEKLKAAHSYNPK+FEWNLK+GRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLD
Sbjct: 365 ESHPVLEKLKAAHSYNPKDFEWNLKNGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLD 424

Query: 195 SAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFVK 254
```

```
           SAFR M+SKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDV+WIFVK
Sbjct: 425 SAFRSMNSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVKWIFVK 484

Query: 255 DVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEKR 314
           DVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII++YKHTTSIFDDF+HYEKR
Sbjct: 485 DVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIATYKHTTSIFDDFSHYEKR 544

Query: 315 Q 315
           Q
Sbjct: 545 Q 545
```

☐ >gi|45361633|ref|NP_989392.1| L hypothetical protein MGC75606 [Xenopus tropicalis]
gi|40675327|gb|AAH64856.1| L Hypothetical protein MGC75606 [Xenopus tropicalis]
Length = 565

```
 Score =  645 bits (1514), Expect = 0.0
 Identities = 207/247 (83%), Positives = 222/247 (89%), Gaps = 8/247 (3%)

Query: 75  QPLPAQPPALAQPQYQSP----QQP--PQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQP 128
           QP+PAQPP ++Q  YQ+P    QQP  PQ RWVAPRNRNAA+GQ GG   D N  G  Q
Sbjct: 305 QPIPAQPPPMSQTPYQNPPPPQQQPQAPQNRWVAPRNRNAAYGQGGGP--DGNPLGGAQS 362

Query: 129 NSAPSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEH 188
           +SAP  ESHPVLEKLKAAHSYNPK+F+WNLK+GRVFIIKSYSEDDIHRSIKYSIWCSTEH
Sbjct: 363 HSAPGNESHPVLEKLKAAHSYNPKDFDWNLKNGRVFIIKSYSEDDIHRSIKYSIWCSTEH 422

Query: 189 GNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDV 248
           GNKRLDSAFR M+ KGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDV
Sbjct: 423 GNKRLDSAFRSMNGKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDV 482

Query: 249 QWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDF 308
           +W+FVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAK VLKII++YKHTTSIFDDF
Sbjct: 483 KWLFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKLVLKIIATYKHTTSIFDDF 542

Query: 309 AHYEKRQ 315
           +HYEKRQ
Sbjct: 543 SHYEKRQ 549
```

☐ >gi|38014398|gb|AAH60445.1| L MGC68505 protein [Xenopus laevis]
Length = 565

```
 Score =  639 bits (1501), Expect = 0.0
 Identities = 205/247 (82%), Positives = 221/247 (89%), Gaps = 8/247 (3%)

Query: 75  QPLPAQPPALAQPQYQSP----QQP--PQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQP 128
           QP+P Q P L+Q QYQ+P    QQP  PQ RWVAPRNRNAA+GQ GG   D N  G  Q
Sbjct: 305 QPIPVQAPPLSQTQYQNPPPPQQQPQAPQNRWVAPRNRNAAYGQGGGP--DGNPLGGAQS 362

Query: 129 NSAPSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEH 188
           ++AP  ESHPVLEKLKAAHSYNPK+F+WNLK+GRVFIIKSYSEDDIHRSIKYSIWCSTEH
Sbjct: 363 HAAPGNESHPVLEKLKAAHSYNPKDFDWNLKNGRVFIIKSYSEDDIHRSIKYSIWCSTEH 422

Query: 189 GNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDV 248
           GNKRLD+AFR M+ KGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDV
Sbjct: 423 GNKRLDNAFRSMNGKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDV 482
```

```
Query: 249 QWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDF 308
           +W+FVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAK VLKII++YKHTTSIFDDF
Sbjct: 483 KWLFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKLVLKIIATYKHTTSIFDDF 542

Query: 309 AHYEKRQ 315
           +HYEKRQ
Sbjct: 543 SHYEKRQ 549
```

☐ >gi|47086617|ref|NP_997878.1| similar to RIKEN cDNA 2210410K23 gene; wu:fi19h06 [Danio re
gi|28422306|gb|AAH46885.1| Similar to RIKEN cDNA 2210410K23 gene [Danio rerio]
Length = 614

```
 Score =  600 bits (1408), Expect = e-170
 Identities = 203/268 (75%), Positives = 221/268 (82%), Gaps = 32/268 (11%)

Query: 76  PLPAQPP-----ALAQ---------PQ-YQS--PQQPPQTRWVAPRNRNAAFGQSGGAGS 118
           P P QPP     +LAQ         PQ YQ+  P  PPQTRWVAPRNRN  +G   G GS
Sbjct: 320 PPPPQPPMPSAQSLAQQMAMQGPPPPQPYQNHAPAPPPQTRWVAPRNRNPGYG---GGGS 376

Query: 119 -DSN---SPGNV-------QPNSAPSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIK 167
            DS+   S G V        P S  ++ESHPVLEKL+AAHSYNPKEF+WNLK+GRVFIIK
Sbjct: 377 VDSSGSSSGGGVGNGGGGGPPGSG-AIESHPVLEKLRAAHSYNPKEFDWNLKNGRVFIIK 435

Query: 168 SYSEDDIHRSIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSP 227
           SYSEDDIHRSIKYSIWCSTEHGNKRLDSAFR ++ KGPVYLLFSVNGSGHFCGVAEM+SP
Sbjct: 436 SYSEDDIHRSIKYSIWCSTEHGNKRLDSAFRAINGKGPVYLLFSVNGSGHFCGVAEMRSP 495

Query: 228 VDYGTSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEK 287
           VDYGTSAGVW+QDKWKGKFDV W+FVKDVPN+QLRHIRLENNDNKPVTNSRDTQEVPLEK
Sbjct: 496 VDYGTSAGVWAQDKWKGKFDVDWLFVKDVPNSQLRHIRLENNDNKPVTNSRDTQEVPLEK 555

Query: 288 AKQVLKIISSYKHTTSIFDDFAHYEKRQ 315
           AKQVLKII++YKHTTSIFDDF+HYEKRQ
Sbjct: 556 AKQVLKIIATYKHTTSIFDDFSHYEKRQ 583
```

☐ >gi|40255135|ref|NP_689971.2| YTH domain family 3 [Homo sapiens]
gi|31419299|gb|AAH52970.1| YTH domain family 3 [Homo sapiens]
Length = 585

```
 Score =  571 bits (1341), Expect = e-161
 Identities = 200/273 (73%), Positives = 218/273 (79%), Gaps = 30/273 (10%)

Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSP 123
           P+ QP P QP        P  AQP Q Q  QQ  Q RWVAPRNR A F Q+ GAGS+
Sbjct: 319 PQQQPQPPQPQQQQGPQPQ-AQPHQVQPQQQQLQNRWVAPRNRGAGFNQNNGAGSE---- 373

Query: 124 GN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRS 177
            N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHRS
Sbjct: 374 -NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHRS 432

Query: 178 IKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVW 237
           IKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VDY   AGVW
Sbjct: 433 IKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDYNAYAGVW 492
```

```
Query: 238 SQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISS 297
           SQDKWKGKF+V+WIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII++
Sbjct: 493 SQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIAT 552

Query: 298 YKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           +KHTTSIFDDFAHYEKRQ      RR     RN
Sbjct: 553 FKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 581
```

☐ >gi|50738020|ref|XP_419227.1| PREDICTED: similar to High glucose-regulated protein 8 [Gallus gallus]

Length = 652

```
 Score =  571 bits (1340), Expect = e-161
 Identities = 202/298 (67%), Positives = 221/298 (74%), Gaps = 52/298 (17%)

Query: 72  PRAQP-LPAQ-----------PPALAQ-------PQYQSPQQP-----------P----- 96
           P AQP LP Q            PP L Q       PQ   PQQP           P
Sbjct: 358 PPAQPVLPPQTIIQQPQPLIQPPTLVQSQLPQQQPQ---PQQPQQQQQGPQQQAQPHQLQQ 414

Query: 97  ---QTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS-VESHPVLEKLKAAHSYNPK 152
              Q RWVAPRNR   F Q+ GAGS++   G V  +S+PS VE HPVLEKLKA ++YNPK
Sbjct: 415 QQLQNRWVAPRNRGVGFSQNNGAGSENFGLGVVSVSSSPSGVEVHPVLEKLKAINNYNPK 474

Query: 153 EFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSV 212
           +F+WNLK+GRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSV
Sbjct: 475 DFDWNLKNGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSV 534

Query: 213 NGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNK 272
           NGSGHFCGVAEMKS VDY   AGVWSQDKWKGKFDV+WIFVKDVPNNQLRHIRLENNDNK
Sbjct: 535 NGSGHFCGVAEMKSVVDYNAYAGVWSQDKWKGKFDVKWIFVKDVPNNQLRHIRLENNDNK 594

Query: 273 PVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           PVTNSRDTQEVPLEKAKQVLKII+++KHTTSIFDDFAHYEKRQ      RR     RN
Sbjct: 595 PVTNSRDTQEVPLEKAKQVLKIIATFKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 648
```

☐ >gi|7705411|ref|NP_057342.1| high glucose-regulated protein 8; high-glucose-regulated protein 9430020E02Rik [Homo sapiens]

gi|5360085|gb|AAD42861.1| NY-REN-2 antigen [Homo sapiens]

gi|6449083|gb|AAF08813.1| high-glucose-regulated protein 8 [Homo sapiens]

Length = 570

```
 Score =  570 bits (1337), Expect = e-161
 Identities = 191/253 (75%), Positives = 209/253 (82%), Gaps = 19/253 (7%)

Query: 75  QPLPAQPPALAQP-----QYQSPQQPPQ-TRWVAPRNRNAAFGQSGGAGSDSNSPGNVQP 128
           QPLP  PP   QP     Q    QQ  Q TRWVAPRNR + FG +G    D N  G  Q
Sbjct: 327 QPLPPPPP---QPAQLSVQ----QQAAQPTRWVAPRNRGSGFGHNGV---DGNGVGQSQA 376

Query: 129 NS--APSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCST 186
            S   PS E HPVLEKL++ ++YNPK+F+WNLK GRVFIIKSYSEDDIHRSIKY+IWCST
Sbjct: 377 GSGSTPS-EPHPVLEKLRSINNYNPKDFDWNLKHGRVFIIKSYSEDDIHRSIKYNIWCST 435

Query: 187 EHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKF 246
           EHGNKRLD+A+R M+ KGPVYLLFSVNGSGHFCGVAEMKS VDY T AGVWSQDKWKG+F
Sbjct: 436 EHGNKRLDAAYRSMNGKGPVYLLFSVNGSGHFCGVAEMKSAVDYNTCAGVWSQDKWKGRF 495
```

```
Query: 247 DVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFD 306
           DV+WIFVKDVPN+QLRHIRLENN+NKPVTNSRDTQEVPLEKAKQVLKII+SYKHTTSIFD
Sbjct: 496 DVRWIFVKDVPNSQLRHIRLENNENKPVTNSRDTQEVPLEKAKQVLKIIASYKHTTSIFD 555

Query: 307 DFAHYEKRQRRRR 319
           DF+HYEKRQR RR
Sbjct: 556 DFSHYEKRQRGRR 568
```

☐ >gi|21751834|dbj|BAC04046.1| L unnamed protein product [Homo sapiens]
Length = 534

Score = 568 bits (1333), Expect = e-160
Identities = 199/273 (72%), Positives = 217/273 (79%), Gaps = 30/273 (10%)

```
Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSP 123
           P+ QP P QP        P  AQP Q Q  QQ  Q RWVAPRNR A F Q+ GAGS+
Sbjct: 268 PQQQPQPPQPQQQQGPQPQ-AQPHQVQPQQQQLQNRWVAPRNRGAGFNQNNGAGSE---- 322

Query: 124 GN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRS 177
            N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHRS
Sbjct: 323 -NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHRS 381

Query: 178 IKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVW 237
           IKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VDY   AGVW
Sbjct: 382 IKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDYNAYAGVW 441

Query: 238 SQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISS 297
           SQDKWKGKF+V+WIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEK KQVLKII++
Sbjct: 442 SQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKVKQVLKIIAT 501

Query: 298 YKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           +KHTTSIFDDFAHYEKRQ      RR     RN
Sbjct: 502 FKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 530
```

☐ >gi|44890479|gb|AAH67040.1| L Ythdf3 protein [Mus musculus]
Length = 585

Score = 568 bits (1333), Expect = e-160
Identities = 200/274 (72%), Positives = 218/274 (79%), Gaps = 32/274 (11%)

```
Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPP-QTRWVAPRNRNAAFGQSGGAGSDSNS 122
           P+ QP P QP        P  AQP Q QS QQP  Q RWVAPRNR   F Q+ G GS+
Sbjct: 319 PQQQPQPPQPQQQQGPQPQ-AQPHQVQS-QQPQLQNRWVAPRNRGTGFNQNNGTGSE--- 373

Query: 123 PGN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHR 176
             N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHR
Sbjct: 374 --NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHR 431

Query: 177 SIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGV 236
           SIKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VDY   AGV
Sbjct: 432 SIKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDYNAYAGV 491

Query: 237 WSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIS 296
           WSQDKWKGKF+V+WIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII+
```

```
Sbjct: 492 WSQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIA 551

Query: 297 SYKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           ++KHTTSIFDDFAHYEKRQ      RR     RN
Sbjct: 552 TFKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 581
```

☐ >gi|26347625|dbj|BAC37461.1| L unnamed protein product [Mus musculus]
Length = 279

```
 Score =  568 bits (1333), Expect = e-160
 Identities = 200/274 (72%), Positives = 218/274 (79%), Gaps = 32/274 (11%)

Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPP-QTRWVAPRNRNAAFGQSGGAGSDSNS 122
           P+ QP P QP       P  AQP Q QS QQP  Q RWVAPRNR   F Q+ G GS+
Sbjct: 13  PQQQPQPPQPQQQQGPQPQ-AQPHQVQS-QQPQLQNRWVAPRNRGTGFNQNNGTGSE--- 67

Query: 123 PGN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHR 176
             N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHR
Sbjct: 68  --NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHR 125

Query: 177 SIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGV 236
           SIKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VDY   AGV
Sbjct: 126 SIKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDYNAYAGV 185

Query: 237 WSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIS 296
           WSQDKWKGKF+V+WIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII+
Sbjct: 186 WSQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIA 245

Query: 297 SYKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           ++KHTTSIFDDFAHYEKRQ      RR     RN
Sbjct: 246 TFKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 275
```

☐ >gi|30962830|gb|AAH52631.1| L Ythdf3 protein [Mus musculus]
Length = 473

```
 Score =  568 bits (1333), Expect = e-160
 Identities = 200/274 (72%), Positives = 218/274 (79%), Gaps = 32/274 (11%)

Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPP-QTRWVAPRNRNAAFGQSGGAGSDSNS 122
           P+ QP P QP       P  AQP Q QS QQP  Q RWVAPRNR   F Q+ G GS+
Sbjct: 207 PQQQPQPPQPQQQQGPQPQ-AQPHQVQS-QQPQLQNRWVAPRNRGTGFNQNNGTGSE--- 261

Query: 123 PGN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHR 176
             N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHR
Sbjct: 262 --NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHR 319

Query: 177 SIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGV 236
           SIKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VDY   AGV
Sbjct: 320 SIKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDYNAYAGV 379

Query: 237 WSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIS 296
           WSQDKWKGKF+V+WIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII+
Sbjct: 380 WSQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIA 439

Query: 297 SYKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
```

```
          ++KHTTSIFDDFAHYEKRQ      RR     RN
Sbjct: 440 TFKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 469
```

>gi|26343683|dbj|BAC35498.1| unnamed protein product [Mus musculus]
gi|34785681|gb|AAH57158.1| Ythdf3 protein [Mus musculus]
Length = 589

```
 Score =  568 bits (1333), Expect = e-160
 Identities = 200/274 (72%), Positives = 218/274 (79%), Gaps = 32/274 (11%)

Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPP-QTRWVAPRNRNAAFGQSGGAGSDSNS 122
           P+ QP P QP       P  AQP Q QS QQP  Q RWVAPRNR   F Q+ G GS+
Sbjct: 323 PQQQPQPPQPQQQQGPQPQ-AQPHQVQS-QQPQLQNRWVAPRNRGTGFNQNNGTGSE--- 377

Query: 123 PGN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHR 176
             N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHR
Sbjct: 378 --NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHR 435

Query: 177 SIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGV 236
           SIKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VDY   AGV
Sbjct: 436 SIKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDYNAYAGV 495

Query: 237 WSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIS 296
           WSQDKWKGKF+V+WIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII+
Sbjct: 496 WSQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIA 555

Query: 297 SYKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           ++KHTTSIFDDFAHYEKRQ      RR     RN
Sbjct: 556 TFKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 585
```

>gi|46048312|ref|NP_766265.2| YTH domain family 3 [Mus musculus]
gi|44890477|gb|AAH67042.1| YTH domain family 3 [Mus musculus]
Length = 596

```
 Score =  568 bits (1333), Expect = e-160
 Identities = 200/274 (72%), Positives = 218/274 (79%), Gaps = 32/274 (11%)

Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPP-QTRWVAPRNRNAAFGQSGGAGSDSNS 122
           P+ QP P QP       P  AQP Q QS QQP  Q RWVAPRNR   F Q+ G GS+
Sbjct: 330 PQQQPQPPQPQQQQGPQPQ-AQPHQVQS-QQPQLQNRWVAPRNRGTGFNQNNGTGSE--- 384

Query: 123 PGN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHR 176
             N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHR
Sbjct: 385 --NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHR 442

Query: 177 SIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGV 236
           SIKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VDY   AGV
Sbjct: 443 SIKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDYNAYAGV 502

Query: 237 WSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIS 296
           WSQDKWKGKF+V+WIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII+
Sbjct: 503 WSQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIA 562

Query: 297 SYKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           ++KHTTSIFDDFAHYEKRQ      RR     RN
```

```
Sbjct: 563 TFKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 592
```

☐ >gi|34855501|ref|XP_342218.1| similar to hypothetical protein FLJ31657 [Rattus norvegicus]
Length = 587

```
 Score =  568 bits (1332), Expect = e-160
 Identities = 198/267 (74%), Positives = 216/267 (80%), Gaps = 28/267 (10%)

Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPP-QTRWVAPRNRNAAFGQSGGAGSDSNS 122
           P+ QP P QP       P  AQP Q QS QQP  Q RWVAPRNR   F Q+ G GS+
Sbjct: 319 PQQQPQPPQPQQQQGPQPQ-AQPHQVQS-QQPQLQNRWVAPRNRGTGFNQNNGTGSE--- 373

Query: 123 PGN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHR 176
             N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHR
Sbjct: 374 --NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHR 431

Query: 177 SIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGV 236
           SIKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VDY   AGV
Sbjct: 432 SIKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDYNAYAGV 491

Query: 237 WSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIS 296
           WSQDKWKGKF+V+WIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII+
Sbjct: 492 WSQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIA 551

Query: 297 SYKHTTSIFDDFAHYEKRQ------RR 317
           ++KHTTSIFDDFAHYEKRQ      RR
Sbjct: 552 TFKHTTSIFDDFAHYEKRQEEEEAMRR 578
```

☐ >gi|26333099|dbj|BAC30267.1| unnamed protein product [Mus musculus]
Length = 589

```
 Score =  566 bits (1328), Expect = e-160
 Identities = 200/274 (72%), Positives = 217/274 (79%), Gaps = 32/274 (11%)

Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPP-QTRWVAPRNRNAAFGQSGGAGSDSNS 122
           P+ QP P QP       P  AQP Q QS QQP  Q RWVAPRNR   F Q+ G GS+
Sbjct: 323 PQQQPQPPQPQQQQGPQPQ-AQPHQVQS-QQPQLQNRWVAPRNRGTGFNQNNGTGSE--- 377

Query: 123 PGN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHR 176
             N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHR
Sbjct: 378 --NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHR 435

Query: 177 SIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGV 236
           SIKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VDY   AGV
Sbjct: 436 SIKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDYNAYAGV 495

Query: 237 WSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIS 296
           WSQDKWKGKF V+WIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII+
Sbjct: 496 WSQDKWKGKFGVKWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIA 555

Query: 297 SYKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           ++KHTTSIFDDFAHYEKRQ      RR     RN
Sbjct: 556 TFKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 585
```

>gi|41019527|sp|Q9Y5A9|HGR8_HUMAN High-glucose-regulated protein 8 (NY-REN-2 antigen) (CLL-a antigen KW-14)
gi|12803469|gb|AAH02559.1| HGRG8 protein [Homo sapiens]
Length = 579

Score = 563 bits (1322), Expect = e-159
Identities = 188/249 (75%), Positives = 206/249 (82%), Gaps = 19/249 (7%)

```
Query: 75  QPLPAQPPALAQP-----QYQSPQQPPQ-TRWVAPRNRNAAFGQSGGAGSDSNSPGNVQP 128
           QPLP  PP   QP     Q    QQ  Q TRWVAPRNR + FG +G    D N  G  Q
Sbjct: 327 QPLPPPPP---QPAQLSVQ----QQAAQPTRWVAPRNRGSGFGHNGV---DGNGVGQSQA 376

Query: 129 NS--APSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCST 186
            S   PS E HPVLEKL++ ++YNPK+F+WNLK GRVFIIKSYSEDDIHRSIKY+IWCST
Sbjct: 377 GSGSTPS-EPHPVLEKLRSINNYNPKDFDWNLKHGRVFIIKSYSEDDIHRSIKYNIWCST 435

Query: 187 EHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKF 246
           EHGNKRLD+A+R M+ KGPVYLLFSVNGSGHFCGVAEMKS VDY T AGVWSQDKWKG+F
Sbjct: 436 EHGNKRLDAAYRSMNGKGPVYLLFSVNGSGHFCGVAEMKSAVDYNTCAGVWSQDKWKGRF 495

Query: 247 DVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFD 306
           DV+WIFVKDVPN+QLRHIRLENN+NKPVTNSRDTQEVPLEKAKQVLKII+SYKHTTSIFD
Sbjct: 496 DVRWIFVKDVPNSQLRHIRLENNENKPVTNSRDTQEVPLEKAKQVLKIIASYKHTTSIFD 555

Query: 307 DFAHYEKRQ 315
           DF+HYEKRQ
Sbjct: 556 DFSHYEKRQ 564
```

>gi|19851923|gb|AAL99921.1| CLL-associated antigen KW-14 [Homo sapiens]
Length = 734

Score = 563 bits (1322), Expect = e-159
Identities = 188/249 (75%), Positives = 206/249 (82%), Gaps = 19/249 (7%)

```
Query: 75  QPLPAQPPALAQP-----QYQSPQQPPQ-TRWVAPRNRNAAFGQSGGAGSDSNSPGNVQP 128
           QPLP  PP   QP     Q    QQ  Q TRWVAPRNR + FG +G    D N  G  Q
Sbjct: 482 QPLPPPPP---QPAQLSVQ----QQAAQPTRWVAPRNRGSGFGHNGV---DGNGVGQSQA 531

Query: 129 NS--APSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCST 186
            S   PS E HPVLEKL++ ++YNPK+F+WNLK GRVFIIKSYSEDDIHRSIKY+IWCST
Sbjct: 532 GSGSTPS-EPHPVLEKLRSINNYNPKDFDWNLKHGRVFIIKSYSEDDIHRSIKYNIWCST 590

Query: 187 EHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKF 246
           EHGNKRLD+A+R M+ KGPVYLLFSVNGSGHFCGVAEMKS VDY T AGVWSQDKWKG+F
Sbjct: 591 EHGNKRLDAAYRSMNGKGPVYLLFSVNGSGHFCGVAEMKSAVDYNTCAGVWSQDKWKGRF 650

Query: 247 DVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFD 306
           DV+WIFVKDVPN+QLRHIRLENN+NKPVTNSRDTQEVPLEKAKQVLKII+SYKHTTSIFD
Sbjct: 651 DVRWIFVKDVPNSQLRHIRLENNENKPVTNSRDTQEVPLEKAKQVLKIIASYKHTTSIFD 710

Query: 307 DFAHYEKRQ 315
           DF+HYEKRQ
Sbjct: 711 DFSHYEKRQ 719
```

☐ >gi|20809771|gb|AAH28994.1| L High glucose-regulated protein 8 [Mus musculus]
Length = 579

Score = 563 bits (1322), Expect = e-159
Identities = 188/249 (75%), Positives = 206/249 (82%), Gaps = 19/249 (7%)

```
Query: 75  QPLPAQPPALAQP-----QYQSPQQPPQ-TRWVAPRNRNAAFGQSGGAGSDSNSPGNVQP 128
           QPLP  PP   QP     Q    QQ  Q TRWVAPRNR + FG +G    D N  G  Q
Sbjct: 327 QPLPPPPP---QPAQLSVQ----QQAAQPTRWVAPRNRGSGFGHNGV---DGNGVGQSQA 376

Query: 129 NS--APSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCST 186
            S   PS E HPVLEKL++ ++YNPK+F+WNLK GRVFIIKSYSEDDIHRSIKY+IWCST
Sbjct: 377 GSGSTPS-EPHPVLEKLRSINNYNPKDFDWNLKHGRVFIIKSYSEDDIHRSIKYNIWCST 435

Query: 187 EHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKF 246
           EHGNKRLD+A+R M+ KGPVYLLFSVNGSGHFCGVAEMKS VDY T AGVWSQDKWKG+F
Sbjct: 436 EHGNKRLDAAYRSMNGKGPVYLLFSVNGSGHFCGVAEMKSAVDYNTCAGVWSQDKWKGRF 495

Query: 247 DVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFD 306
           DV+WIFVKDVPN+QLRHIRLENN+NKPVTNSRDTQEVPLEKAKQVLKII+SYKHTTSIFD
Sbjct: 496 DVRWIFVKDVPNSQLRHIRLENNENKPVTNSRDTQEVPLEKAKQVLKIIASYKHTTSIFD 555

Query: 307 DFAHYEKRQ 315
           DF+HYEKRQ
Sbjct: 556 DFSHYEKRQ 564
```

☐ >gi|15928654|gb|AAH14797.1| L High glucose-regulated protein 8 [Mus musculus]
gi|26327473|dbj|BAC27480.1| L unnamed protein product [Mus musculus]
gi|26350823|dbj|BAC39048.1| L unnamed protein product [Mus musculus]
Length = 579

Score = 563 bits (1322), Expect = e-159
Identities = 188/249 (75%), Positives = 206/249 (82%), Gaps = 19/249 (7%)

```
Query: 75  QPLPAQPPALAQP-----QYQSPQQPPQ-TRWVAPRNRNAAFGQSGGAGSDSNSPGNVQP 128
           QPLP  PP   QP     Q    QQ  Q TRWVAPRNR + FG +G    D N  G  Q
Sbjct: 327 QPLPPPPP---QPAQLSVQ----QQAAQPTRWVAPRNRGSGFGHNGV---DGNGVGQSQA 376

Query: 129 NS--APSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCST 186
            S   PS E HPVLEKL++ ++YNPK+F+WNLK GRVFIIKSYSEDDIHRSIKY+IWCST
Sbjct: 377 GSGSTPS-EPHPVLEKLRSINNYNPKDFDWNLKHGRVFIIKSYSEDDIHRSIKYNIWCST 435

Query: 187 EHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKF 246
           EHGNKRLD+A+R M+ KGPVYLLFSVNGSGHFCGVAEMKS VDY T AGVWSQDKWKG+F
Sbjct: 436 EHGNKRLDAAYRSMNGKGPVYLLFSVNGSGHFCGVAEMKSAVDYNTCAGVWSQDKWKGRF 495

Query: 247 DVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFD 306
           DV+WIFVKDVPN+QLRHIRLENN+NKPVTNSRDTQEVPLEKAKQVLKII+SYKHTTSIFD
Sbjct: 496 DVRWIFVKDVPNSQLRHIRLENNENKPVTNSRDTQEVPLEKAKQVLKIIASYKHTTSIFD 555

Query: 307 DFAHYEKRQ 315
           DF+HYEKRQ
Sbjct: 556 DFSHYEKRQ 564
```

>gi|30841028|ref|NP_663368.2| high glucose-regulated protein 8 [Mus musculus]
gi|26330093|dbj|BAC28785.1| unnamed protein product [Mus musculus]
Length = 579

Score = 563 bits (1322), Expect = e-159
Identities = 188/249 (75%), Positives = 206/249 (82%), Gaps = 19/249 (7%)

```
Query: 75  QPLPAQPPALAQP-----QYQSPQQPPQ-TRWVAPRNRNAAFGQSGGAGSDSNSPGNVQP 128
           QPLP  PP   QP     Q    QQ  Q TRWVAPRNR + FG +G    D N  G  Q
Sbjct: 327 QPLPPPPP---QPAQLSVQ----QQAAQPTRWVAPRNRGSGFGHNGV---DGNGVGQSQA 376

Query: 129 NS--APSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCST 186
            S   PS E HPVLEKL++ ++YNPK+F+WNLK GRVFIIKSYSEDDIHRSIKY+IWCST
Sbjct: 377 GSGSTPS-EPHPVLEKLRSINNYNPKDFDWNLKHGRVFIIKSYSEDDIHRSIKYNIWCST 435

Query: 187 EHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKF 246
           EHGNKRLD+A+R M+ KGPVYLLFSVNGSGHFCGVAEMKS VDY T AGVWSQDKWKG+F
Sbjct: 436 EHGNKRLDAAYRSMNGKGPVYLLFSVNGSGHFCGVAEMKSAVDYNTCAGVWSQDKWKGRF 495

Query: 247 DVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFD 306
           DV+WIFVKDVPN+QLRHIRLENN+NKPVTNSRDTQEVPLEKAKQVLKII+SYKHTTSIFD
Sbjct: 496 DVRWIFVKDVPNSQLRHIRLENNENKPVTNSRDTQEVPLEKAKQVLKIIASYKHTTSIFD 555

Query: 307 DFAHYEKRQ 315
           DF+HYEKRQ
Sbjct: 556 DFSHYEKRQ 564
```

>gi|50759678|ref|XP_417730.1| PREDICTED: similar to High-glucose-regulated protein 8 (NY-REI
antigen) (CLL-associated antigen KW-14) [Gallus gallus]
Length = 1210

Score = 559 bits (1312), Expect = e-158
Identities = 190/264 (71%), Positives = 214/264 (81%), Gaps = 31/264 (11%)

```
Query: 62  GGQVGLKVSRPRAQPLPAQPPALAQPQYQSPQQPPQ-----TRWVAPRNRNAAFGQSGGA 116
           GGQ        ++QPLP  PP   QP   +P   PQ     TRWVAPRNR + FGQ+G
Sbjct: 707 GGQ--------QSQPLPPPPP---QP---TPLPVPQPAAQPTRWVAPRNRGSGFGQNGTE 752

Query: 117 GSDSNSPGNV---QPNS--APSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSE 171
           G      G V   QP++  APS E HPVLEKL++ ++YNPK+F+WN K GRVFIIKSYSE
Sbjct: 753 G------GGVGAAQPSTGTAPS-EPHPVLEKLRSINNYNPKDFDWNPKHGRVFIIKSYSE 805

Query: 172 DDIHRSIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYG 231
           DDIHRSIKY+IWCSTEHGNKRLD+A+R M+ KGPVYLLFSVNGSGHFCGVAEMKS VDY
Sbjct: 806 DDIHRSIKYNIWCSTEHGNKRLDAAYRSMNGKGPVYLLFSVNGSGHFCGVAEMKSAVDYN 865

Query: 232 TSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQV 291
           T AGVWSQDKWKG+FDV+WIFVKDVPN+QLRHIRLENN+NKPVTNSRDTQEVPLEKAKQV
Sbjct: 866 TCAGVWSQDKWKGRFDVRWIFVKDVPNSQLRHIRLENNENKPVTNSRDTQEVPLEKAKQV 925

Query: 292 LKIISSYKHTTSIFDDFAHYEKRQ 315
           LKII++YKHTTSIFDDF+HYEKRQ
Sbjct: 926 LKIIATYKHTTSIFDDFSHYEKRQ 949
```

>gi|21732274|emb|CAD38530.1| hypothetical protein [Homo sapiens]

```
          Length = 638

 Score =  557 bits (1308), Expect = e-157
 Identities = 198/276 (71%), Positives = 217/276 (78%), Gaps = 36/276 (13%)

Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSP 123
           P+ QP P QP        P  AQP Q Q  QQ  Q RWVAPRNR A F Q+ GAGS+
Sbjct: 372 PQQQPQPPQPQQQQGPQPQ-AQPHQVQPQQQQLQNRWVAPRNRGAGFNQNNGAGSE---- 426

Query: 124 GN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRS 177
            N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHRS
Sbjct: 427 -NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHRS 485

Query: 178 IKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVD---YGTSA 234
           IKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VD   Y   A
Sbjct: 486 IKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDCNAY---A 542

Query: 235 GVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKI 294
           GVWSQDKWKGKF+V+WIFVKDVPNNQLRHIRLEN+DNKPVTNSRDTQEVPLEKAKQVLKI
Sbjct: 543 GVWSQDKWKGKFEVKWIFVKDVPNNQLRHIRLENSDNKPVTNSRDTQEVPLEKAKQVLKI 602

Query: 295 ISSYKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           I+++KHTTSI DDFAHYEKRQ      RR     RN
Sbjct: 603 IATFKHTTSILDDFAHYEKRQEEEEAMRR----ERN 634


 Score = 23.5 bits (48), Expect = 15017
 Identities = 6/7 (85%), Positives = 7/7 (100%)

Query: 312 EKRQRRR 318
           E+RQRRR
Sbjct: 42  ERRQRRR 48
```

☐ >gi|41054079|ref|NP_956164.1| L Similar to RIKEN cDNA 9130022A11 gene; wu:fi35c09 [Danio re
gi|28277558|gb|AAH45342.1| L Similar to RIKEN cDNA 9130022A11 gene [Danio rerio]

```
          Length = 600

 Score =  544 bits (1276), Expect = e-153
 Identities = 194/297 (65%), Positives = 211/297 (71%), Gaps = 64/297 (21%)

Query: 76  PLPAQPPALAQPQYQ-----SPQQP--------------------------P--QTRWV 101
           PLP Q    QPQ+Q     SPQ P                          P  Q RWV
Sbjct: 316 PLPPQH----QPQHQQLQVQSPQHPQHLPPGPPHHHSQPGPPQPLHPSQAQNPLIQNRWV 371

Query: 102 APRNRNAAFGQ-SG------GAGSDSNSPGNVQPNSAPSV-ESHPVLEKLKAAHSYNPKE 153
           APRNR   F Q SG      G G         V  +S+PS  E HPVLEKLKA ++YNPK+
Sbjct: 372 APRNRGTMFNQNSGMDNFGLGTG--------VPMSSSPSSNEVHPVLEKLKALNNYNPKD 423

Query: 154 FEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVN 213
           F+W LK+GRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLD A+R +S+KGP+YLLFSVN
Sbjct: 424 FDWTLKNGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLDGAYRSLSAKGPLYLLFSVN 483

Query: 214 GSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKP 273
           GSGHFCGVAEMKS VDY   AGVWSQDKWKGKF+V+WIFVKDVPNNQLRHIRLENNDNKP
Sbjct: 484 GSGHFCGVAEMKSTVDYNAYAGVWSQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNDNKP 543
```

```
Query: 274 VTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           VTNSRDTQEVPLEKAKQVLKII+++KHTTSIFDDFAHYEKRQ      RR     RN
Sbjct: 544 VTNSRDTQEVPLEKAKQVLKIIATFKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 596
```

☐ >gi|47223342|emb|CAG04203.1| unnamed protein product [Tetraodon nigroviridis]
Length = 587

Score = 534 bits (1253), Expect = e-150
Identities = 183/245 (74%), Positives = 201/245 (82%), Gaps = 21/245 (8%)

```
Query: 77  LPAQ--PPALAQPQYQSPQQ--PPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSA- 131
           L +Q  PP L Q   Q PQQ  PP  RWVAPRNR   F   GG            P SA
Sbjct: 346 LSSQAGPP-LHQ---QHPQQAGPPPNRWVAPRNRGEGFCLGGGV----------PLSAS 390

Query: 132 P-SVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGN 190
           P S E HPVLEKL+A ++YNPK+F+W+LK+GRVFIIKSYSEDDIHRSIKYSIWCSTEHGN
Sbjct: 391 PCSGEVHPVLEKLQALNNYNPKDFDWSLKNGRVFIIKSYSEDDIHRSIKYSIWCSTEHGN 450

Query: 191 KRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQW 250
           KRLD A+  + SKGP+YLLFSVNGSGHFCGVAEM+SPVDY   AGVWSQDKWKGKF+V+W
Sbjct: 451 KRLDGAYHSLGSKGPLYLLFSVNGSGHFCGVAEMRSPVDYNAFAGVWSQDKWKGKFEVKW 510

Query: 251 IFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAH 310
           IF+KDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVL+II++YKHTTSIFDDFAH
Sbjct: 511 IFIKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLRIIATYKHTTSIFDDFAH 570

Query: 311 YEKRQ 315
           YEKRQ
Sbjct: 571 YEKRQ 575
```

☐ >gi|41053800|ref|NP_956544.1| L hypothetical protein MGC56224 [Danio rerio]
gi|28839108|gb|AAH47846.1| L Hypothetical protein MGC56224 [Danio rerio]
Length = 596

Score = 533 bits (1250), Expect = e-150
Identities = 183/257 (71%), Positives = 206/257 (80%), Gaps = 28/257 (10%)

```
Query: 75  QPLP------AQPPALAQPQYQSPQ--QPPQ-TRWVAPRNRNAAFGQS-GGAGSDSNSPG 124
            PLP      A PP L+Q     P   QP Q TRWV PRNR   FG + GG G    SP
Sbjct: 333 HPLPPGGQPGAVPPQLSQ----GPPVSQPSQPTRWVPPRNRANGFGDAAGGPG---QSP- 384

Query: 125 NVQPNSA------PSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSI 178
              PNS        P+ E HPVLEKL+  ++YNPK+F+WN K GRVFIIKSYSEDDIHRSI
Sbjct: 385 ---PNSGMGGITVPA-EPHPVLEKLRMVNNYNPKDFDWNPKHGRVFIIKSYSEDDIHRSI 440

Query: 179 KYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWS 238
           KY+IWCSTEHGNKRLD+A+R +++KGP YLLFSVNGSGHFCGVAEM+SPVDY T AGVWS
Sbjct: 441 KYNIWCSTEHGNKRLDAAYRSLANKGPPYLLFSVNGSGHFCGVAEMRSPVDYNTCAGVWS 500

Query: 239 QDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSY 298
           QDKWKG+FDV+WIFVKDVPN+QLRHIRLENN+NKPVTNSRDTQEVPL+KA+QVLKII+SY
Sbjct: 501 QDKWKGRFDVRWIFVKDVPNSQLRHIRLENNENKPVTNSRDTQEVPLDKARQVLKIIASY 560

Query: 299 KHTTSIFDDFAHYEKRQ 315
           KHTTSIFDDF+HYEKRQ
```

```
Sbjct: 561 KHTTSIFDDFSHYEKRQ 577
```

☐ >gi|38086386|ref|XP_205340.3| similar to High glucose-regulated protein 8 [Mus musculus]
Length = 579

```
 Score =  514 bits (1206), Expect = e-144
 Identities = 176/247 (71%), Positives = 199/247 (80%), Gaps = 19/247 (7%)

Query: 75  QPLPAQPPALAQP-----QYQSPQQPPQ-TRWVAPRNRNAAFGQSGGAGSDSNSPGNVQP 128
           QPLP  PP   QP     Q    QQ  Q T WVAPRNR + FG +G AG   N  G  Q
Sbjct: 327 QPLPPPPP---QPAQISVQ----QQAAQPTCWVAPRNRGSGFGHNGVAG---NGVGQSQA 376

Query: 129 --NSAPSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCST 186
             +S PS E HPVLEKL++ ++YN K+F+WNLK GRVFIIKSYSEDDIH SIKY+IWCST
Sbjct: 377 GSDSTPS-EPHPVLEKLRSINNYNTKDFDWNLKHGRVFIIKSYSEDDIHLSIKYNIWCST 435

Query: 187 EHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKF 246
           E GNK LD+ +R M+ KGP YLLFSVNGSGHFCGVAEMKS VDY T AG+WSQDKWKG+F
Sbjct: 436 EQGNKILDATYRSMNGKGPAYLLFSVNGSGHFCGVAEMKSAVDYNTCAGLWSQDKWKGRF 495

Query: 247 DVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFD 306
           +V+WIFVKD+PN+QL+HIRLENN+NKPVTNSRDTQEVPLEKAKQVLKII+SYKHTTSIFD
Sbjct: 496 NVRWIFVKDIPNSQLQHIRLENNENKPVTNSRDTQEVPLEKAKQVLKIIASYKHTTSIFD 555

Query: 307 DFAHYEK 313
           DF+HYEK
Sbjct: 556 DFSHYEK 562
```

☐ >gi|50418347|gb|AAH78013.1| Unknown (protein for MGC:82537) [Xenopus laevis]
Length = 493

```
 Score =  491 bits (1151), Expect = e-137
 Identities = 163/225 (72%), Positives = 187/225 (83%), Gaps = 20/225 (8%)

Query: 92  PQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS-VESHPVLEKLKAAHSYN 150
           P  P  TRW A RNR           S+       Q   APS  E HPVLEKL++ ++YN
Sbjct: 276 PHAP--TRWSAHRNRI----------SE-------QTQLAPSTAEPHPVLEKLRSVNNYN 316

Query: 151 PKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLF 210
           PK+F+++LK GRVFI+KSYSEDDIHRSIKY+IWCSTEHGNKRLD+A+R ++ KGP+YLLF
Sbjct: 317 PKDFDFSLKLGRVFIVKSYSEDDIHRSIKYNIWCSTEHGNKRLDAAYRSLNGKGPLYLLF 376

Query: 211 SVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENND 270
           SVNGSGHFCGVAEM+S VDY T AGVWSQDKWKG+FDV+W+FVKDVPN QLRHIRLENND
Sbjct: 377 SVNGSGHFCGVAEMRSAVDYNTCAGVWSQDKWKGRFDVRWLFVKDVPNGQLRHIRLENND 436

Query: 271 NKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEKRQ 315
           NKPVTNSRDTQEVPLEKA+QVL+II+SYKHTTSIFDDF+HYEKRQ
Sbjct: 437 NKPVTNSRDTQEVPLEKARQVLRIIASYKHTTSIFDDFSHYEKRQ 481
```

☐ >gi|46329541|gb|AAH68959.1| MGC83235 protein [Xenopus laevis]
Length = 494

```
 Score =  488 bits (1145), Expect = e-136
 Identities = 168/239 (70%), Positives = 195/239 (81%), Gaps = 26/239 (10%)

Query: 81  PPALAQ--PQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQ--PNSAPSVES 136
           PP L Q  P   +PQ P  TRW A RNR++   Q+             Q  P++A   E
Sbjct: 266 PPMLQQTLPT--APQAP--TRWSAHRNRSSE--QT-------------QLPPSNA---EP 303

Query: 137 HPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLDSA 196
           HPVLEKL+  ++YNPK+F+++LK GRVFIIKSYSEDDIHRSIKY++WCSTEHGNKRLD+A
Sbjct: 304 HPVLEKLRLVNNYNPKDFDFSLKLGRVFIIKSYSEDDIHRSIKYNVWCSTEHGNKRLDAA 363

Query: 197 FRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFVKDV 256
           FR ++ KGP+YLLFSVNGSGHFCGVAEM S VDY T AGVWSQDKWKG+FDV+W+FVKDV
Sbjct: 364 FRSLNGKGPLYLLFSVNGSGHFCGVAEMCSAVDYNTCAGVWSQDKWKGRFDVRWLFVKDV 423

Query: 257 PNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEKRQ 315
           PN QLRHIRLENN+NKPVTNSRDTQEVPLEKA+QVL+II+SYKHTTSIFDDF+HYEKRQ
Sbjct: 424 PNGQLRHIRLENNENKPVTNSRDTQEVPLEKARQVLRIIASYKHTTSIFDDFSHYEKRQ 482
```

☐ >gi|18605766|gb|AAH22932.1| L Ythdf3 protein [Mus musculus]
Length = 175

```
 Score =  466 bits (1093), Expect = e-130
 Identities = 147/175 (84%), Positives = 158/175 (90%), Gaps = 10/175 (5%)

Query: 156 WNLKSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGS 215
           WNLK+GRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGS
Sbjct: 1   WNLKNGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGS 60

Query: 216 GHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVT 275
           GHFCGVAEMKS VDY   AGVWSQDKWKGKF+V+WIFVKDVPNNQLRHIRLENNDNKPVT
Sbjct: 61  GHFCGVAEMKSVVDYNAYAGVWSQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNDNKPVT 120

Query: 276 NSRDTQEVPLEKAKQVLKIISSYKHTTSIFDDFAHYEKRQ------RRRRWCARN 324
           NSRDTQEVPLEKAKQVLKII+++KHTTSIFDDFAHYEKRQ      RR     RN
Sbjct: 121 NSRDTQEVPLEKAKQVLKIIATFKHTTSIFDDFAHYEKRQEEEEAMRR----ERN 171
```

☐ >gi|47230021|emb|CAG10435.1| unnamed protein product [Tetraodon nigroviridis]
Length = 762

```
 Score =  462 bits (1084), Expect = e-129
 Identities = 168/261 (64%), Positives = 189/261 (72%), Gaps = 45/261 (17%)

Query: 78  PAQPPALAQ-PQY---QSP--------QQPPQ-TRWVAPRNRNAAFGQSGGAGSDSNSPG 124
           P QP  L Q PQ    Q P        QQ PQ TRWVAPRNR   FG   G     N PG
Sbjct: 309 PGQP-GLVQIPQVSLSQGPPPPSHHQQQQAPQPTRWVAPRNRANGFGDPSG-----NGPG 362

Query: 125 NVQPNSA-----PSV--ESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRS 177
              P S+     P V  E HPVLEKL+  ++YNPK+F+WN K GRVFIIKSYSEDDIHRS
Sbjct: 363 QSPPTSSGVAVVPGVPSEPHPVLEKLRMVNNYNPKDFDWNPKQGRVFIIKSYSEDDIHRS 422

Query: 178 IKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVW 237
           IKY+IWCSTEHGNKRLD+A+R + +KGP+YLLFSVNGSGHFCGVAEM+SPVDY TS
Sbjct: 423 IKYNIWCSTEHGNKRLDAAYRSLGAKGPLYLLFSVNGSGHFCGVAEMRSPVDYNTS---- 478
```

```
Query: 238 SQDKWKGKFDV---QWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKI 294
              +W+     V   Q      DVPN+QLRHIRLENN+NKPVTNSRDTQEVPL+KA+QVLKI
Sbjct: 479 ---RWR----VVAGQ-----DVPNSQLRHIRLENNENKPVTNSRDTQEVPLDKARQVLKI 526

Query: 295 ISSYKHTTSIFDDFAHYEKRQ 315
           I+ YKHTTSIFDDF+HYEKRQ
Sbjct: 527 IAGYKHTTSIFDDFSHYEKRQ 547
```

☐ >gi|47229164|emb|CAG03916.1| unnamed protein product [Tetraodon nigroviridis]
Length = 541

```
 Score =  440 bits (1031), Expect = e-122
 Identities = 165/264 (62%), Positives = 180/264 (68%), Gaps = 62/264 (23%)

Query: 74  AQPL--------PAQPPALAQPQYQ--SPQQPPQTRWVAPRNRNAAFGQSGGAGS-DSNS 122
           AQ L         P  PP    P YQ  S    PQTRWVAPR+RN  +G   G GS DS+
Sbjct: 310 AQSLVQQMTMPGPPPPP----PSYQNHSSAPTPQTRWVAPRSRNFCYG---GGGSLDSSG 362

Query: 123 P----GNV-------QPNSAPSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSE 171
                G V         P    P  ESHPVLEKL+AAHSYNP+EF+WNLK+GRVFIIKSYSE
Sbjct: 363 SSTAGGGVGNGGGGFTPE--PGAESHPVLEKLRAAHSYNPREFDWNLKNGRVFIIKSYSE 420

Query: 172 DDIHRSIKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYG 231
           DDIHRSIKYSIWCSTEHGNKRLDSAFR M+SKGPVYLLFSVNGSGHFCGVA  ++ +
Sbjct: 421 DDIHRSIKYSIWCSTEHGNKRLDSAFRAMNSKGPVYLLFSVNGSGHFCGVA--RNAL--- 475

Query: 232 TSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQV 291
            +A V                           RHIRLENNDNKPVTNSRDTQEVPLEKAKQV
Sbjct: 476 -AASV------------------------RHIRLENNDNKPVTNSRDTQEVPLEKAKQV 509

Query: 292 LKIISSYKHTTSIFDDFAHYEKRQ 315
           LKII+ YKHTTSIFDDF+HYEK+Q
Sbjct: 510 LKIITQYKHTTSIFDDFSHYEKKQ 533
```

☐ >gi|16551561|dbj|BAB71122.1| L unnamed protein product [Homo sapiens]
Length = 543

```
 Score =  432 bits (1012), Expect = e-119
 Identities = 153/213 (71%), Positives = 169/213 (79%), Gaps = 20/213 (9%)

Query: 72  PRAQPLPAQP-------PALAQP-QYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSP 123
           P+ QP P QP        P  AQP Q Q  QQ  Q RWVAPRNR A F Q+ GAGS+
Sbjct: 319 PQQQPQPPQPQQQQGPQPQ-AQPHQVQPQQQQLQNRWVAPRNRGAGFNQNNGAGSE---- 373

Query: 124 GN----VQPNSA-PS-VESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRS 177
            N    V P SA PS VE HPVLEKLKA ++YNPK+F+WNLK+GRVFIIKSYSEDDIHRS
Sbjct: 374 -NFGLGVVPVSASPSSVEVHPVLEKLKAINNYNPKDFDWNLKNGRVFIIKSYSEDDIHRS 432

Query: 178 IKYSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVW 237
           IKYSIWCSTEHGNKRLD+A+R ++ KGP+YLLFSVNGSGHFCGVAEMKS VDY   AGVW
Sbjct: 433 IKYSIWCSTEHGNKRLDAAYRSLNGKGPLYLLFSVNGSGHFCGVAEMKSVVDYNAYAGVW 492

Query: 238 SQDKWKGKFDVQWIFVKDVPNNQLRHIRLENND 270
           SQDKWKGKF+V+WIFVKDVPNNQLRHIRLENN+
Sbjct: 493 SQDKWKGKFEVKWIFVKDVPNNQLRHIRLENNE 525
```

☐ >gi|47207024|emb|CAF91623.1| unnamed protein product [Tetraodon nigroviridis]
Length = 494

Score = 409 bits (958), Expect = e-112
Identities = 124/136 (91%), Positives = 134/136 (98%)

```
Query: 180 YSIWCSTEHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVWSQ 239
           YSIWCSTEHGNKRLDSA+R M++KGPVYLLFSVNGSGHFCGVAEM+SPVDYGTSAGVW+Q
Sbjct: 348 YSIWCSTEHGNKRLDSAYRAMNAKGPVYLLFSVNGSGHFCGVAEMRSPVDYGTSAGVWAQ 407

Query: 240 DKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISSYK 299
           DKWKGKFDV W+FVKDVPN+QLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKII++YK
Sbjct: 408 DKWKGKFDVDWLFVKDVPNSQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIIATYK 467

Query: 300 HTTSIFDDFAHYEKRQ 315
           HTTSIFDDF+HYEKRQ
Sbjct: 468 HTTSIFDDFSHYEKRQ 483
```

☐ >gi|24649883|ref|NP_733067.1| L CG6422-PB [Drosophila melanogaster]
gi|23172237|gb|AAN14031.1| CG6422-PB [Drosophila melanogaster]
Length = 699

Score = 348 bits (814), Expect = 2e-94
Identities = 127/205 (61%), Positives = 153/205 (74%), Gaps = 25/205 (12%)

```
Query: 126 VQPNSA----PSVESHPVLEKLKAAHSYNPKEFEWNLK---SGRVFIIKSYSEDDIHRSI 178
           V+  SA    P V+S  VL++LK  ++YNPK  +  LK   S R F+IKSYSEDDIHRSI
Sbjct: 342 VEATSATEELP-VDSQLVLDELKDKNNYNPKVLD--LKKAGSARFFVIKSYSEDDIHRSI 398

Query: 179 KYSIWCSTEHGNKRLDSAFR--------CMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDY 230
           KY IWCST+HGNKRLD AF+         M       L FSVNGSGHFCG+A+M +PVDY
Sbjct: 399 KYEIWCSTDHGNKRLDDAFKERHEEGGNIM-------LFFSVNGSGHFCGMAQMMTPVDY 451

Query: 231 GTSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQ 290
            +++ VWSQDKW+GKF V+WI+VKDVPN  LRHIRLENN+NK VTNSRDTQEVP +K  +
Sbjct: 452 NSTSSVWSQDKWRGKFKVKWIYVKDVPNGTLRHIRLENNENKSVTNSRDTQEVPNDKGIE 511

Query: 291 VLKIISSYKHTTSIFDDFAHYEKRQ 315
           VL+I+ SY H+TSIFDDF HYEK+Q
Sbjct: 512 VLQILHSYNHSTSIFDDFFHYEKKQ 536
```

☐ >gi|21356147|ref|NP_651322.1| L CG6422-PA [Drosophila melanogaster]
gi|7301251|gb|AAF56381.1| L CG6422-PA [Drosophila melanogaster]
gi|17862686|gb|AAL39820.1| L LD44979p [Drosophila melanogaster]
Length = 700

Score = 348 bits (814), Expect = 2e-94
Identities = 127/205 (61%), Positives = 153/205 (74%), Gaps = 25/205 (12%)

```
Query: 126 VQPNSA----PSVESHPVLEKLKAAHSYNPKEFEWNLK---SGRVFIIKSYSEDDIHRSI 178
           V+  SA    P V+S  VL++LK  ++YNPK  +  LK   S R F+IKSYSEDDIHRSI
```

```
Sbjct: 343 VEATSATEELP-VDSQLVLDELKDKNNYNPKVLD--LKKAGSARFFVIKSYSEDDIHRSI 399

Query: 179 KYSIWCSTEHGNKRLDSAFR--------CMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDY 230
           KY IWCST+HGNKRLD AF+          M       L FSVNGSGHFCG+A+M +PVDY
Sbjct: 400 KYEIWCSTDHGNKRLDDAFKERHEEGGNIM-------LFFSVNGSGHFCGMAQMMTPVDY 452

Query: 231 GTSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQ 290
            +++ VWSQDKW+GKF V+WI+VKDVPN  LRHIRLENN+NK VTNSRDTQEVP +K  +
Sbjct: 453 NSTSSVWSQDKWRGKFKVKWIYVKDVPNGTLRHIRLENNENKSVTNSRDTQEVPNDKGIE 512

Query: 291 VLKIISSYKHTTSIFDDFAHYEKRQ 315
           VL+I+ SY H+TSIFDDF HYEK+Q
Sbjct: 513 VLQILHSYNHSTSIFDDFFHYEKKQ 537
```

☐ >gi|31202859|ref|XP_310378.1| ENSANGP00000005606 [Anopheles gambiae]
gi|21293824|gb|EAA05969.1| ENSANGP00000005606 [Anopheles gambiae str. PEST]
Length = 331

Score = 348 bits (814), Expect = 2e-94
Identities = 148/258 (57%), Positives = 177/258 (68%), Gaps = 29/258 (11%)

```
Query: 74  AQPLPAQ-P-PALAQPQYQSPQQPPQTRWVAPR--NRNAAFGQSGGAGSDSNSPGNVQPN 129
           A P+P++ P P  AQ Q Q  QQP  T    P   +RN   G S G  S S   G+   N
Sbjct: 78  ADPVPSKWPTPGQAQIQ-Q--QQPSGT----PSSSDRNN--GPSAGTNSGSGGSGS---N 125

Query: 130 SAPS--------VESHPVLEKLKAAHSYNPKEFEWNLKS---GRVFIIKSYSEDDIHRSI 178
           +A           ES  +L++LK  ++YNP   +  LK+    R F+IKSYSEDDIHRSI
Sbjct: 126 AASGESEMALKLAESQKILDQLKTKNNYNPASLDL-LKTVDLARFFVIKSYSEDDIHRSI 184

Query: 179 KYSIWCSTEHGNKRLDSAFRCMSSKG-PVYLLFSVNGSGHFCGVAEMKSPVDYGTSAGVW 237
           KY IWCSTEHGN+RLD AFR    KG  VYL FSVNGSGHFCGVA+M + VDY +++ VW
Sbjct: 185 KYEIWCSTEHGNQRLDQAFREREEKGGTVYLFFSVNGSGHFCGVAQMMTAVDYNSNSSVW 244

Query: 238 SQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQVLKIISS 297
           SQDKWKG F V+WI+VKDVPN+ LRHIRLENN+NK +TNSRDTQEVP  K  QVL+II S
Sbjct: 245 SQDKWKGTFKVRWIYVKDVPNSHLRHIRLENNENKSMTNSRDTQEVPNAKGIQVLQIIHS 304

Query: 298 YKHTTSIFDDFAHYEKRQ 315
           ++H +SIFDDF HYEKRQ
Sbjct: 305 FEHQSSIFDDFQHYEKRQ 322
```

☐ >gi|25012679|gb|AAN71434.1| RE55836p [Drosophila melanogaster]
Length = 699

Score = 348 bits (814), Expect = 2e-94
Identities = 127/205 (61%), Positives = 153/205 (74%), Gaps = 25/205 (12%)

```
Query: 126 VQPNSA----PSVESHPVLEKLKAAHSYNPKEFEWNLK---SGRVFIIKSYSEDDIHRSI 178
           V+  SA    P V+S  VL++LK  ++YNPK  +  LK    S R F+IKSYSEDDIHRSI
Sbjct: 342 VEATSATEELP-VDSQLVLDELKDKNNYNPKVLD--LKKAGSARFFVIKSYSEDDIHRSI 398

Query: 179 KYSIWCSTEHGNKRLDSAFR--------CMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDY 230
           KY IWCST+HGNKRLD AF+          M       L FSVNGSGHFCG+A+M +PVDY
Sbjct: 399 KYEIWCSTDHGNKRLDDAFKERHEEGGNIM-------LFFSVNGSGHFCGMAQMMTPVDY 451
```

```
Query: 231 GTSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENNDNKPVTNSRDTQEVPLEKAKQ 290
           +++ VWSQDKW+GKF V+WI+VKDVPN  LRHIRLENN+NK VTNSRDTQEVP +K  +
Sbjct: 452 NSTSSVWSQDKWRGKFKVKWIYVKDVPNGTLRHIRLENNENKSVTNSRDTQEVPNDKGIE 511

Query: 291 VLKIISSYKHTTSIFDDFAHYEKRQ 315
           VL+I+ SY H+TSIFDDF HYEK+Q
Sbjct: 512 VLQILHSYNHSTSIFDDFFHYEKKQ 536
```

☐ >gi|34871864|ref|XP_232772.2| L similar to High-glucose-regulated protein 8 (NY-REN-2 antige
[Rattus norvegicus]
Length = 660

```
 Score =  317 bits (740), Expect = 7e-85
 Identities = 114/169 (67%), Positives = 126/169 (74%), Gaps = 19/169 (11%)

Query: 75  QPLPAQPPALAQP-----QYQSPQQPPQ-TRWVAPRNRNAAFGQSGGAGSDSNSPGNVQP 128
           QPLP  PP   QP     Q    QQ  Q TRWVAPRNR + FG +G    D N  G  Q
Sbjct: 425 QPLPPPPP---QPAQLSVQ----QQAAQPTRWVAPRNRGSGFGHNGV---DGNGVGQSQA 474

Query: 129 NS--APSVESHPVLEKLKAAHSYNPKEFEWNLKSGRVFIIKSYSEDDIHRSIKYSIWCST 186
            S   PS E HPVLEKL++ ++YNPK+F+WNLK GRVFIIKSYSEDDIHRSIKY+IWCST
Sbjct: 475 GSGSTPS-EPHPVLEKLRSINNYNPKDFDWNLKHGRVFIIKSYSEDDIHRSIKYNIWCST 533

Query: 187 EHGNKRLDSAFRCMSSKGPVYLLFSVNGSGHFCGVAEMKSPVDYGTSAG 235
           EHGNKRLD+A+R M+ KGPVYLLFSVNGSGHFCGVAEMKS VDY T AG
Sbjct: 534 EHGNKRLDAAYRSMNGKGPVYLLFSVNGSGHFCGVAEMKSAVDYNTCAG 582
```

☐ >gi|42407463|dbj|BAD10396.1| putative rubisco subunit binding-protein beta subunit [Oryza sa
(japonica cultivar-group)]
gi|42407930|dbj|BAD09069.1| putative rubisco subunit binding-protein beta subunit [Oryza sati
(japonica cultivar-group)]
Length = 624

```
 Score =  258 bits (603), Expect = 2e-67
 Identities = 100/169 (59%), Positives = 119/169 (70%), Gaps = 19/169 (11%)

Query: 159 KSGRVFIIKSYSEDDIHRSIKYSIWCSTEHGNKRLDSAFR--------CMSSKGPVYLLF 210
           K+ R FIIKSYSED++H+SIKY +W ST +GNK+LDSA+R        C     P++LLF
Sbjct: 383 KNARFFIIKSYSEDNVHKSIKYGVWASTTNGNKKLDSAYREAKEKEEHC-----PIFLLF 437

Query: 211 SVNGSGHFCGVAEMKSPVDYGTSAGVWSQDKWKGKFDVQWIFVKDVPNNQLRHIRLENND 270
           SVN S  FCGVAEM  PVD+  S   W QDKW G+F V+W  VKDVPNN  RHI LENND
Sbjct: 438 SVNASAQFCGVAEMIGPVDFEKSVDYWQQDKWTGQFPVKWHIVKDVPNNLFRHIILENND 497

Query: 271 NKPVTNSRDTQEVPLEKAKQVLKIISSYK-H--TTSIFDDFAHYEKRQR 316
           NKPVTNSRDTQEV LE+  ++LKI   +K H    SI DDF  YE+R+R
Sbjct: 498 NKPVTNSRDTQEVKLEQGMEMLKI---FKDHEEDASILDDFDFYEERER 543
```

☐ >gi|7020460|dbj|BAA91138.1| L unnamed protein product [Homo sapiens]
Length = 197

```
 Score =  257 bits (599), Expect = 7e-67
 Identities = 81/81 (100%), Positives = 81/81 (100%)
```

```
Query: 74  AQPLPAQPPALAQPQYQSPQQPPQTRWVAPRNRNAAFGQSGGAGSDSNSPGNVQPNSAPS 133
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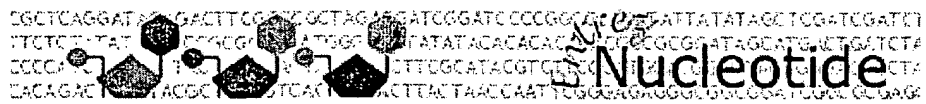

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  TITLE     Direct Submission
  JOURNAL   Submitted (06-FEB-2001) Yoshinao Muro, Nagoya University School of
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            466-8550, Japan (E-mail:ymuro@med.nagoya-u.ac.jp, Tel:81527442314,
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Jul 27 2004 07:08:51

Review

Polymyositis and dermatomyositis associated with malignancy: a 30-year retrospective study

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Abstract

Background Polymyositis and dermatomyositis in association with malignancy are paraneoplastic syndromes, but the incidence, treatment and factors that predict associated cancer and its prognosis all remain unclear.

Patients and Method During the 30-year period 1969–99, we treated 64 patients who had polymyositis (including two with cancer) and 28 patients who had dermatomyositis (including 10 with cancer). We compared the clinical findings of the patients who had cancer with the findings of those who did not have cancer.

Results The risk of cancer is significantly higher in dermatomyositis and somewhat higher in polymyositis. An increased cancer risk was found in male patients with dermatomyositis who were older than 50 years. Cancer was diagnosed within 4 years before or after the diagnosis of polymyositis or dermatomyositis, and usually within 1 year. An operation was not possible in many of the patients with cancer because of the advanced stage of the disease.

Conclusion Our findings suggest that early discovery of malignancy is critical in cases of polymyositis and dermatomyositis.

Introduction

Polymyositis (PM) is a disorder of unknown cause characterized by an inflammatory myopathy involving skeletal muscle and, less commonly, cardiac muscle. When characteristic cutaneous lesions accompany myositis, the diagnosis is dermatomyositis (DM).[1] Improved immunohistochemical analysis of muscle biopsy specimens has revealed important differences between PM and DM[2,3] and has led to the inclusion of amyopathic dermatomyositis in the same paraneoplastic syndrome.[4]

The first case of PM associated with gastric cancer was reported by Stertz in 1916,[5] and in the same year, DM in association with breast cancer was reported.[6] An increased incidence of malignancy in patients with PM or DM has been reported by many authors,[7–23] but the extent of this trend remains unclear. Estimates of the associated risk vary markedly (between 6% and 60%), probably because of the different specialties involved in treating patients with PM or DM, including internal medicine, neurology, collagen vascular division, dermatology, and pediatrics. Patients with DM have a greater frequency of malignancy than the general population. However, PM does not seem to be associated with a greatly increased risk of malignancy.

We compared the clinical data of patients who had PM or DM and cancer with the data of patients who had PM or DM but no cancer.

Patients and Methods

We treated 64 patients with PM (23 male and 41 female) and 28 patients with DM (six male and 22 female) during the 30-year period 1969–99. Two patients with PM and 10 with DM had malignancy. The diagnosis of PM or DM was based on the criteria of Bohan and Peter:[1] (1) symmetric proximal muscle weakness; (2) increased serum creatine kinase value; (3) presence of typical cutaneous lesions such as heliotropic rash, Gottron papules, malar erythema, poikiloderma on sun-exposed areas, and periungual or cuticular changes; (4) typical electromyographic findings (low-amplitude, short-duration polyphasic neuromuscular unit potentials, fibrillation, positive sharp waves, increased insertional voltages, and spontaneous high-frequency discharges); and (5) muscle biopsy findings showing degenerative and inflammatory changes. A diagnosis of PM was based on criteria 1, 2, 4, and 5, and a diagnosis of DM was based on all five criteria.

After the diagnosis of PM or DM, the patients who had malignancy were monitored with complete blood tests, including tests for tumor markers, pulmonary radiography, gastrointestinal tract examination (including computed tomography or magnetic resonance imaging), otolaryngologic examination, gynecologic examination in the women, and urologic examination. Muscle biopsy was performed in all cases; however, only 56 muscle biopsy specimens could be examined because the color of the stain had faded in the older cases. Of the 56 cases examined,

Table 1 Demographic data of 92 patients with polymyositis or dermatomyositis

	Polymyositis		Dermatomyositis	
	With cancer	Without cancer	With cancer	Without cancer
Patients (*n*)	2	62	10	18
Sex (*n*)				
Male	1	22	4	2
Female	1	40	6	16
Age at onset (y)				
Male	75	26–84	51–74	32–62
Female	54	14–72	58–72	19–68
Mean age ± SD (y)				
Male	44.4 ± 15.9	65.5 ± 10.0	47.0 ± 21.2	
Female	48.6 ± 19.7	59.0 ± 8.1	53.1 ± 15.7	
Deaths (*n*)	2	13	10	4

37 were PM (two malignant) and 19 were DM (six malignant). Muscle biopsies preceded treatment in all cases. Muscle biopsy specimens were stained with hematoxylin-eosin, modified Gomori trichrome, and reduced nicotinamide adenine dinucleotide tetrazolium reductase. To exclude accidental complications, we selected patients in whom malignancy was discovered within several years before or after the diagnosis of PM or DM and in whom cancer treatment was effective for the symptoms for PM or DM.[24]

Mean and SD were calculated with standard statistical procedures. A statistical analysis was performed with two-way analysis of variance and the Mann–Whitney *U*-test.

Results

Demographic data for all patients are provided in Table 1, and the clinical courses for the 12 patients with cancer are outlined in Table 2. One patient with DM who had two malignancies was excluded because the malignancies occurred 17 and 26 years after DM was diagnosed.

Sex

In the patients without cancer, the number of female patients exceeded that of male patients. However, in patients with DM, male sex was a risk factor (Table 1) in that four of the six male patients had cancer.

Age

The patients with PM and DM who had cancer were older than those without cancer, but there were no significant differences (Table 1).

Incidence of malignancy

The frequency of malignancy was 3% in the patients with PM and 36% in those with DM. The tumor site varied. The uterus, lung, and stomach were affected slightly more often, but the difference was not significant (Table 2).

Interval to tumor discovery

Almost all cancers were discovered within 4 years after the diagnosis of PM or DM, and two were diagnosed before the onset of DM. The most common interval was within 1 year of PM or DM being diagnosed. In three patients, tumors were discovered at autopsy (Table 2).

Cause of death

In the cases of PM without cancer, circulatory disorders (myocardial infarction and congestion) were the most frequent cause of death (47%). In the cases of DM with cancer, pneumonia was the most frequent cause (50%).

Therapy

The therapies are summarized in Table 2. Only four patients were able to undergo an operation, including the two patients whose cancers preceded the onset of DM. Three patients received chemotherapy; one of these also underwent radiotherapy, and one also had operation. Six patients did not receive any therapy for cancer because of the advanced stage of the tumor. The effectiveness of prednisolone for myositis and cutaneous lesions was identical for the cancer and noncancer cases early in the disease process (Table 2).

Survival rate

The survival rate of the patients who had PM without cancer was 80% at 6 years, but in those who had PM with cancer it was 0% at 4 years. In the patients who had DM without cancer, the survival rate was 73.6% at 6 years, but in the patients who had DM with cancer it was 10% at 5 years (Fig. 1).

Muscle biopsy

In general, histologic changes were observed in PM but only slightly in DM. However, blood vessel changes occurred in DM rather than in PM. In PM, although the number of cancer cases was limited, interstitial and interfiber inflammatory cell infiltration was greater than in the PM cases without cancer.

Table 2 Clinical course of 12 patients with polymyositis or dermatomyositis who had a malignancy

Case	Age at onset (y)	Sex	Diagnosis	CK, IU/l	Time from disease onset to cancer	Cancer site	Therapy for cancer	Effect of therapy for PM/DM*	Time from disease onset to death	Cause of death
1	54	F	PM	1083	1 year (autopsy)	Ovary	None	–	1 year 1 month	Pneumonia
2	75	M	PM	2317	4 years (autopsy)	Stomach	None	±	4 years	Bleeding (RP)
3	51	F	DM	809	11 months (autopsy)	Pharynx	None	±	1 year	Bleeding (PX)
4	64	F	DM	ND	2 years 2 months	Pancreas	None	±	2 years 6 months	Bleeding (IP)
5	51	M	DM	557	6 months	Lung	Chemo + radi	–	1 year 4 months	Cancer
6	74	M	DM	850	2 months	Stomach	Chemo	–	7 months	Cancer
7	69	M	DM	2050	2 years 7 months	Bladder	Operation, chemo	±	3 years	Pneumonia
8	51	F	DM	ND	11 months	Unknown	–	±	1 year	Pneumonia
9	58	F	DM	543	3 months	Uterus	Operation	+	12 years	
10	58	F	DM	163	~3 years	Uterus	Operation	+	4 years	Pneumonia
11	68	M	DM	342	~2 years	Prostate	Operation	–	3 years	Interstitial pneumonia
12	72	F	DM	815	2 months	Lung	–	–	3 years	Peritonitis

Chemo = chemotherapy; CK = creatine kinase; DM = dermatomyositis; IP = intraperitoneal; ND = not determined; PM = polymyositis; PX = pharynx; radi = radiation; RP = retroperitoneal.

–, poor; +, good; ±, moderate.

*All patients were treated with prednisolone.

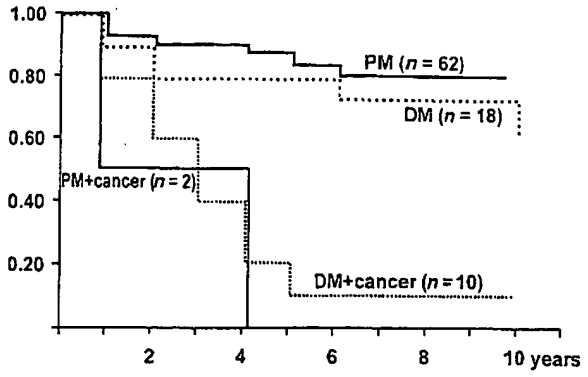

Figure 1 Survival rate in polymyositis (PM) and dermatomyositis (DM) (Kaplan-Meier test)

In the DM cases with cancer, variations in fiber diameter and targetoid fiber ($P < 0.05$) were observed, and in the DM cases without cancer, regeneration and inflammatory cell infiltration were prominent (Table 3).

Discussion

Polymyositis or DM with malignancy is one of the paraneoplastic syndromes, but, unlike other such disorders, a specific autoantibody has not been discovered. In this study, we attempted to determine the malignancy rate, optimal treatment for cancer, prognosis for patients with cancer, and the factors that might predict malignancy.

Is there a true association between PM or DM and cancer?

An increased incidence of cancer in PM or DM has been reported by many authors.[7–23] However, we are aware of only three control studies. Manchul *et al.*[10] studied 71 patients who were referred to a Canadian rheumatology department over a 15-year period, and compared the prevalence of malignancy at presentation with that in matched controls. The study identified 15 antecedent or concurrent cancers in the case-control arm and five in the control group, but there was no increase in the number of subsequent cancers observed in the cohort arm. Lakhanpal *et al.*[12] identified 115 patients with myositis who were referred to their hospital between 1965 and 1974. They compared age-, sex-, and geographically matched controls. Overall, cancer developed in 29 patients with myositis and in 20 controls, a result that was not statistically significant. Lyon *et al.*[14] surveyed 322 patients from 1985 to 1986. They compared patients who had PM or DM with sibling controls. They found five cancers in the myositis group and three in the control group, a result that was not statistically significant.

More recently, five larger population-based cohort studies were carried out. Sigurgeirsson *et al.*[15] studied 788 myositis cases in Sweden from 1963 through 1983. Their report

Table 3 Histopathologic changes in polymyositis and dermatomyositis

	Polymyositis				Dermatomyositis			
	Without cancer (n = 35)		With cancer (n = 2)		Without cancer (n = 13)		With cancer (n = 6)	
Change	n	%	n	%	n	%	n	%
Muscle fibers								
Variation in fiber diameter	35	100	2	100	7	54	6	100
Internal nuclei	12	34	1	50	7	54	3	50
Necrosis	29	83	1	50	7	54	4	67
Granular change	17	49	1	50	7	23	2	33
Vacuolation	22	63	1	50	3	23	1	17
Targetoid fiber	26	74	1	50	3	15	4	67*
Ghost fiber	15	43	1	50	2	8	1	17
Regeneration (basophilia)	26	74	2	100	1	69	2	33
Perifascular atrophy	2	6	0	–	1	9	8	0
Inflammatory cell infiltration								
Perivascular	18	51	1	50	8	62	3	50
Interstitial	24	69	2	100	9	69	3	50
Interfiber	21	60	2	100	10	77	2	33
Blood vessels								
Capillary necrosis	0	–	1	50	1	8	0	–
Intimal hyperplasia	4	11	0	–	2	15	1	17
Arterial necrosis	1	3	0	–	2	15	1	17
Other								
Interstitial fibrosis	25	71	2	100	10	77	4	67

*$P < 0.05$.

suggested that the risk of cancer was higher in patients with PM or DM. Chow *et al.*[18] analyzed 539 patients with myositis in Denmark between 1977 and 1989. This cohort study of patients with DM or PM revealed a significantly higher cancer risk within 2 years of follow up, consistent with a paraneoplastic syndrome, but no convincing evidence of greater risk among long-term survivors. Zantos *et al.*[16] analyzed 1078 myositis cases (565 PM and 513 DM). They concluded that the cancer risk was high both before and after diagnosis of DM, but in PM, the cancer risk was higher only after diagnosis of myositis. Airio *et al.*[17] analyzed 175 PM and 71 DM cases. They concluded that the relative risk of cancer was very high in the first year after diagnosis of DM. Hill *et al.*[23] analyzed 1532 myositis cases (618 DM and 914 PM) from Sweden, Denmark, and Finland. They identified cancer in 198 of the 618 cases of DM and in 137 of the 914 cases of PM. They suggested that DM was strongly associated with cancer and that PM was modestly associated with an increased risk of malignant disease.

We did not conduct a control study, but our study findings, as well as those discussed above, suggest that the risk of cancer is significantly higher in DM, and somewhat higher in PM.

Does the risk of cancer depend on age?

Regarding the correlation between the risk of cancer in PM or DM and age, Hochberg *et al.*[13] reported that the age-specific mortality rate was higher in patients older than 55 years. Marie *et al.*[21] reported that in elderly patients, complete remission of PM or DM was less frequent (13.6% vs. 41.1%) and the mortality rate (47.8% vs. 7.3%) was higher. In our report, cancer risk was extremely high in male patients older than 50, but the difference was not significant.

Is the breast the most frequent cancer site?

Barnes and Mawr[25] reported that the breast was the most frequent tumor site in a study of 258 DM cases (17.8%). Sigurgeirsson *et al.*[13] reported that the colon (including the rectum) and the lung were the most frequent cancer sites in a study of 750 patients with PM or DM. Hatada *et al.*[26] reported that stomach cancer was the most frequent cancer site in DM in Japan (25.4%). Hill *et al.*[23] reported that the highest risks of cancer after the diagnosis of DM were for ovarian, lung, pancreatic, stomach, and colorectal cancers and for lymphomas. Patients with PM had an increased risk of lung and bladder cancers and non-Hodgkin lymphoma. However, our study found no significant correlation because of the limited number of patients studied.

What is the cause of death?

Cardiac infarction is the most frequent cause of death in PM without cancer because the cardiac muscles are more severely affected than in DM. Respiratory failure (pneumonia and

pneumonitis) is the most frequent cause of death in DM with or without cancer, because interstitial pneumonitis is common in DM.

Summary of treatment

Treatment of PM or DM with cancer is identical to that of general cancer. Moreover, a diagnosis of cancer does not alter the treatment of myositis in PM or DM. The interval from onset of PM or DM to the discovery of cancer was almost identical to that from disease onset to death; however, cancer was diagnosed first in two patients (cases 10 and 11, Table 2), and one patient (case 9) was a long-term survivor. These findings suggest that in many patients an operation is not an option at the time of diagnosis of the cancer or that clinicians fail to examine the patient adequately for cancer. In three of our cases, malignancy was discovered at autopsy, suggesting that cancers associated with PM or DM progress more slowly than general cancers. These findings suggest that the most important therapeutic challenge is the early discovery of malignancy.

Survival rate in PM or DM with or without malignancy

Survival rates have been discussed in several studies; however, only a few that compare survival in PM or DM with or without cancer are described here. Benbassat *et al.*[11] reported that the survival rate in patients with PM or DM was 50% at 4 years. Lakhanpal *et al.*[12] determined that the survival rate was 56% at 5 years in patients with PM or DM. Hochberg *et al.*[13] found a survival rate of 79% at 5 years in patients with PM or DM. Basset-Seguin *et al.*[27] reported a survival rate of 57% at 3 years in DM and of 25% at 2 years in DM with cancer. Sigurgeirsson *et al.*[15] found a survival rate of 60% in PM and 57% in DM with or without cancer at 5 years. Marie *et al.*[21] reported that the mortality rate was significantly higher in elderly patients with PM or DM than in younger patients (47.8% vs. 7.3%, $P = 0.0001$). Eleven elderly patients (47.8%) died within a median period of 2 months after diagnosis of PM or DM (range, 1–20 months). However, younger patients died within a median period of 42 months after diagnosis of PM or DM (range, 6 months to 8 years). Davis and Ahmed[19] reported that mortality from ovarian cancer was 100%, and the mean survival time from diagnosis was 11 months (range, 0–28 months). The patient with zero survival time died shortly after a diagnostic laparotomy. We conclude that an association with malignancy or late onset results in decreased survival rates in both PM and DM.

What predicts PM or DM associated with malignancy?

Many authors have attempted to determine factors useful for predicting malignancy in PM or DM. One potential predictive factor, interstitial pneumonitis, remains controversial.[28–31] There is a report that acute exacerbation of interstitial pneumonitis is a risk factor for malignancy.[32] Lakhanpal *et al.*[12] found that a low serum creatine kinase level was a risk factor for malignancy in PM or DM. Basset-Seguin *et al.*[27] concluded that cutaneous necrosis and an increased erythrocyte sedimentation rate (> 40 mm in 1 h) were potential predictive signs of cancer in adults with DM. Rose and Walton[33] reported that factors associated with paraneoplastic DM included age, a decreased serum albumin level, and an increased C-reactive protein value. Dourmishev[22] characterized the differences between idiopathic and paraneoplastic DM. Paraneoplastic DM is more often associated with poikiloderma, ulcerations, and an increased erythrocyte sedimentation rate than idiopathic DM. Marie *et al.*[21] found no clinical or laboratory information predictive of cancer in elderly patients with PM or DM. In our study, muscle biopsy specimens were compared, but the results were not conclusive.

Conclusion

In the treatment of PM or DM associated with cancer, the most important challenge is the prompt detection of malignancy. It is hoped that further investigations will reveal a specific autoantibody for this complication, as has been the case with the other paraneoplastic disorders.

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Dermatomyositis associated with angiotropic lymphoma

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Summary

We describe a 64-year-old man with dermatomyositis sine myositis who presented with unusual cutaneous plaques and nodules. Initial investigations failed to reveal evidence of malignancy. Eighteen months later he became systemically unwell and repeat biopsies from the nodules confirmed angiotropic T-cell lymphoma. Cutaneous lymphoma is rarely reported with dermatomyositis and in the previously reported cases, mycosis fungoides was the variant seen. This is the first report of angiotropic T-cell lymphoma associated with dermatomyositis.

Report

The association of malignancy with dermatomyositis is well established. We report a 64-year-old man who had an angiotropic T-cell lymphoma in association with dermatomyositis. He had been diagnosed as having dermatomyositis sine myositis, on the basis of a classic presentation accompanied by Gottron's papules (Fig. 1), skin pathology demonstrating vacuolar alteration at the dermo-epidermal junction with a mild to moderate lymphohistiocytic infiltrate in the papillary dermis and around adnexal structures, and a positive Jo-1. At that time he was also noted to have erythematous, indurated plaques and nodules on the buttocks, upper arms and thighs. Extensive investigations for underlying malignancy were negative. These included blood tests, oesophagoscopy, colonoscopy, ultrasound scan of abdomen, computed tomography (CT) of the chest, abdomen and pelvis, CT of the sinuses and a barium enema. Creatinine kinase (CPK) testing was also normal. He was initially treated with a combination of hydroxychloroquine and a reducing dose of oral steroids with good effect.

Eighteen months later, the patient presented with malaise, weight loss, diarrhoea and rigors. Examination revealed new discrete large indurated erythematous plaques and nodules on both arms, his upper back and his right thigh. He had no evidence of lymphadenopathy or hepatosplenomegaly. Laboratory tests showed a haemoglobin of 8.2 g/dL, normocytic, normochromic, white cell count 3.6, platelets of 77. Renal function was normal. Potassium was 2.4 (normal range, 3.5–4.5). Liver function tests were as follows: albumin 21 (normal range, 35–50), alkaline phosphatase 597 (normal range, 40–120), γ-glutaryl transferase 156 (normal range, 10–55), lactate dehydrogenase 842 (normal range, 230–450), aspartate aminotransferase 73 (normal range, 7–40). Erythrocyte sedimentation rate was 69 mm/ h, C-reactive protein was 24 (normal range, 0–10). Anitnuclear antigen was positive $>1:160<1:640$ with a nucleolar pattern, antigliadin antibody was 75.4 (normal range, 0–5) and antiendomysial antibody was positive. Immunoglobulins: IgA 4.25 (normal range, 0.48–3.44), IgG 13 (normal range, 6.4–15.2), IgM 2.52 (normal range, 0.29–1.86), with no monoclonal bands.

Radiological investigations included a CT abdomen, which revealed small bowel wall thickening. Ileoscopy was normal, a biopsy showed small bowel villous atrophy. Colonoscopy showed discrete ulcers throughout the large bowel. Colonic biopsy revealed widespread lymphocytic colitis with focal cryptitis and ulceration, consistent with coeliac disease. There was no histological evidence of lymphoma in bowel biopsies, including PCR testing for T-cell rearrangements.

Repeated skin biopsies were taken of the indurated plaques and nodules as follows: initially epidermal spongiosus with necrotic keratinocytes and a

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Figure 1 Infiltrated Gottrons papules seen over metacarpophalangeal joints. Splinter haemorrhages are evident.

lymphohistiocytic infiltrate in the papillary dermis. Later biopsies showed a lymphophagocytic vasculitis with zonal necrosis. There were large atypical lymphocytes in a perivascular distribution (Fig. 2a). Immunostaining showed a prominent T-cell cytotoxic infiltrate, staining positive for CD3 and CD8 (Fig. 2b). CD4 and CD20 stains were negative. Biopsy showed scattered and grouped lymphoid cells demonstrating infiltration of the subcutaneous fat with pronounced angiotropism. Venous thrombosis was seen with patchy fat infarction. The lymphoid cells were large with copious eosinophilic cytoplasm, prominent nucleoli and mitoses. These findings were diagnostic of an angiotropic lymphoma.

During the course of his illness, the patient improved on prednisolone 60 mg per day and a gluten-free diet, demonstrating weight gain, less frequent diarrhoea and pyrexias. However, his clinical condition deteriorated with swinging pyrexias, progressive weight loss and ongoing diarrhoea. He was unfit for chemotherapy and palliation was the method of treatment until death.

There is a well recognized association between dermatomyositis and malignancy.[1] Recent data reports that 32% of patients with dermatomyositis develop a malignancy, which may pre- or postdate the development of dermatomyositis. Hill *et al.* report 13% of these patients developing cancers which precede the diagnosis of dermatomyositis, the majority of which occur within 2 years of diagnosis. The association between dermatomyositis and lymphomas is very rare. Only two cases of dermatomyositis associated with cutaneous T-cell lymphoma have been previously reported.[2,3] These cases reported the development of mycosis fungoides, rather than an aggressive fatal lymphoma as in this case. This

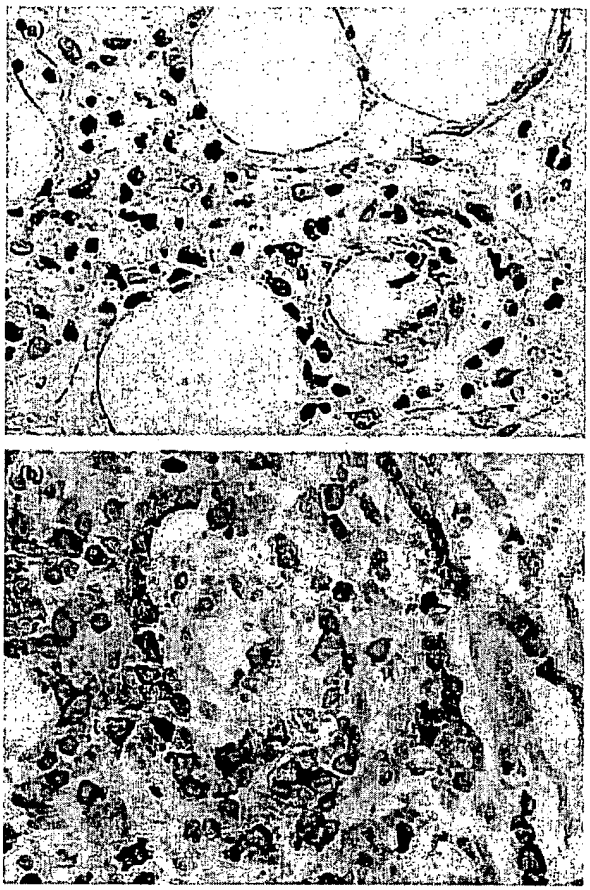

Figure 2 (a) Oedematous dermis with scattered atypical lymphoid cells in a perivascular distribution and infiltrating between fat cells. Patchy infarction of fat with necrotic tissue. (b) Atypical cells infiltrating blood vessels walls and the connective tissue, staining with CD3 and CD8, seen in the blood vessel wall and in a perivascular distribution.

is the first report of an aggressive, cytotoxic cutaneous T-cell lymphoma associated with dermatomyositis.

This patient was also diagnosed with coeliac disease, the diagnosis of which postdated the initial development of plaques and nodules. He had a lymphocytic colitis on biopsy but no evidence of lymphoma despite multiple biopsies and the use of PCR testing for gene rearrangements. This presentation would be unusual for enteropathy associated T-cell lymphoma (EATCL) but this diagnosis must be considered in the differential diagnosis.

Malignant lymphomas deriving from peripheral T or natural killer (NK) cells are rare tumours in Europe accounting for less than 10% of all cases of malignant lymphoma.[4] The types of peripheral T-cell lymphoma associated with a cytotoxic phenotype are angiocentric lymphoma, angiotropic lymphoma, aggressive NK

leukaemia, intestinal T-cell lymphoma and anaplastic large cell lymphoma.[5] Cytotoxic phenotype tends to be associated with more aggressive clinical behaviour. The pancytopenia seen in this case may represent haemophagocytosis, which is well documented in association with these tumours.

We report the case of a man with a classic presentation of dermatomyositis who had puzzling cutaneous plaques and nodules. He developed coeliac disease and his general condition deteriorated. The plaques and nodules increased in size and number. Despite multiple nondiagnostic biopsies and a high degree of clinical suspicion, a diagnosis of angiotropic lymphoma was made 18 months after presentation. We suggest that lymphoma should be borne in mind in patients with dermatomyositis presenting with unusual cutaneous plaques and nodules.

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Dermatomyositis, Carcinoma of Colon and Meningioma in the Same Patient

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Abstract

Dermatomyositis and carcinoma of colon were diagnosed in a 66-year-old woman. Meticulous physical examination excluded further systemic or cutaneous involvement. The musculocutaneous disorders responded well to daily oral corticosteroid, and the malignant tumor was totally removed surgically. After a seven-year follow-up of actual dermatomyositis controlled by maintenance doses of prednisone ranging from 5 to 15 mg daily, the patient developed a meningioma. Current concepts and data regarding various aspects of the combination between dermatomyositis and tumors are discussed. To our knowledge, this is the first reported case of meningioma associated with dermatomyositis.

Abbreviations: PM: polymyositis, DM: dermatomyositis, ESR: erythrocyte sedimentation rate, CK: creatine phosphokinase, SGOT: serum glutamic oxalacetic transaminase, LDH: lactate dehydrogenase, CRP: C reactive protein, ANF: antinuclear factor, CT: computed tomography

Key words: dermatomyositis; polymyositis; carcinoma of colon; meningioma; malignancy

Introduction

The association of a large spectrum of tumors with PM and, particularly, DM is well documented (1–18). Any organ of the body may be affected and there is no characteristic type or site (19). However, a review of the literature revealed only a single case of meningioma in a patient with PM (15). We report an interesting and unusual case of a female with DM who developed meningioma in addition to a carcinoma of colon.

Case Report

A 73-year-old white woman, who was born in Tunisia and has been living in Israel for 24 years, was referred for neurological consultation because of headache, dysphagia, and general weakness.

Her medical history dated back to the age of 66, when she was first hospitalized in the geriatric department with gradual worsening of muscular strength and a skin rash. The physical examination revealed a fair-skinned woman of normal stature with severe muscular weakness and pain of the neck and upper and lower limbs of four months duration, as well as an erythematous eruption on her face involving the forehead and malar regions, typical purplish-blue and edematous upper eyelids, telangiectatic areas on the upper chest, and red patches over the arms and legs. The patient had difficulty in rising from a sitting position, climbing stairs, and lifting her hands. Results of the remainder of the clinical examination were negative or normal. No hepatosplenomegaly or lymphadenopathy were found on palpation. Her parents, five children, and other relatives were not affected by any skin or systemic disorders.

A comprehensive laboratory investigation detected the following pathological findings: ESR 80 mm/hr, CK 353 IU/L (normal 15 to 110 IU/L), SGOT 65 IU/L (normal up to 27 IU/L), LDH 400 IU/L (normal 140 to 300 IU/L), positive ANF, and positive rheumatoid factor. Radiographic evaluation of the hip revealed calcium deposition under the skin in the gluteal and upper thigh area (Fig. 1). The electromyogram showed myopathic and neurologi-

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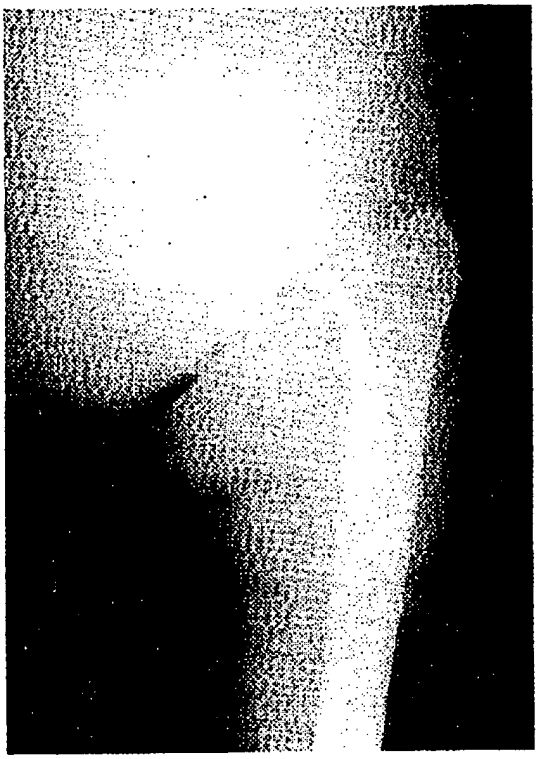

Fig. 1. Calcium deposition under the skin in the gluteal and the upper thigh region.

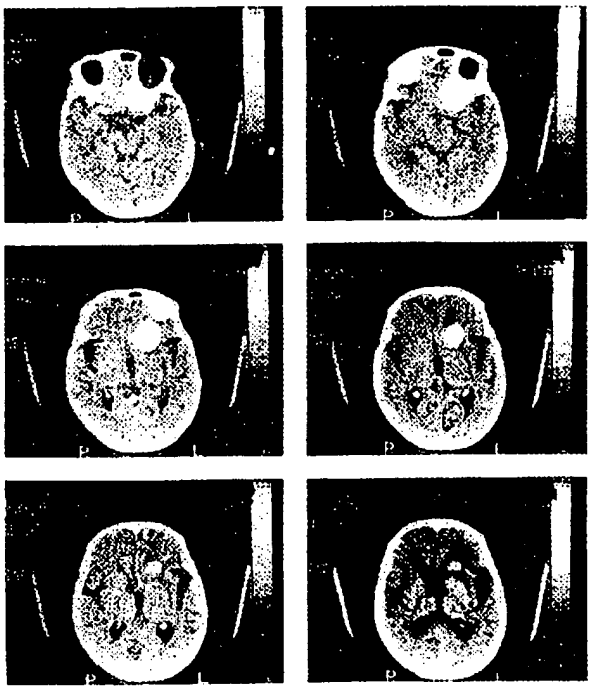

Fig. 2. Calcifying process compatible with temporal meningioma. Brain CT scan.

cal alterations consistent with DM. Histological examination of a biopsy specimen from the skin of the right arm and the deltoid muscle demonstrated cutaneous and muscular changes characteristic of DM. A barium enema, performed as part of a detailed radiological search for neoplasms, known to be frequently associated with DM (1–15, 19), revealed an asymptomatic stricture in the rectosigmoid area, confirmed to be a tumor by colonscopy. Its pathological examination disclosed a fairly well differentiated adenocarcinoma of the colon. Results of routine laboratory tests, immunoglobulin (IgG, IgA, IgM) levels, antistreptolysin O titer, CRP, serologic test for syphilis, LE test, mycological examinations, ECG, and chest X-rays were normal or negative.

Dramatic control of the musculo-cutaneous findings was achieved with a daily dose of 60 mg prednisone. The skin rash cleared in a few days, the muscle strength increased progressively and was almost totally regained, and the ESR and enzyme levels returned to normal within five weeks. In view of these improvements, the dosage of prednisone was gradually decreased. The malignant mass was completely removed by anterior resection of the sigmoid colon with end to end anastomosis. No intraabdominal metastasis or second tumor was detected during the surgical procedure. The patient was discharged in a good general condition after an uneventful postoperative course. However, four months later, a spontaneous relapse of the DM required more aggressive therapy. Consequently, the daily maintenance dose of 10 mg prednisone was increased to 40 mg/day. Following clinical and biochemical remission, the dosage of prednisone was slowly tapered during the successive months to a daily maintenance dose of 5 mg/day. The patient was regularly seen at the outpatient clinic with characteristic mild to moderate fluctuations in the intensity of her medical signs and symptoms responsive to a prednisone dosage ranging from 10 to 15 mg daily.

Seven years after the onset of DM, while the patient was treated for several weeks with 10 mg prednisone per day because the reappearance of muscular tenderness on motion and discomfort during hair dressing with ESR of 30 mm/hr, after prolonged remission in the status of her illness maintained under adequate control by a low daily dose of 5 mg prednisone. She was readmitted to

the geriatric department, with neurological findings of central facialis, hemiparesis, hypoestesia, upper limb hyperreflexia, positive bilateral Marineski sign, amnestic aphasia, mild cognitive disorders with memory disturbance, and arithmetic errors. The brain CT scan revealed a left temporal meningioma (Fig. 2). At this stage, the patient and her relatives refused any suggestion of neurosurgical intervention. She succumbed three months later after a cerebrovascular accident and coma.

Discussion

The nature of the relationship between different types of tumors and DM is incompletely understood (8). Probably, both coincidental and true combinations exist (8). It has been stated that oncogenes (21, 22), hypersensitivity reactions (21), and/or immune processes (21) may play important roles in the association. At the present time, sufficient data is unavailable to substantiate any of these theories (21, 22), and the complex mechanisms involved in each process remain to be explained (21). The great majority of individuals with DM have been found to have only one space-occupying mass (1–22); in a relatively small fraction of cases, more than one tumor was detected (9, 11, 16, 20, 23). Multiple neoplasms may occur in the same organ, in paired viscera, in viscera of the same system, or, to a much lesser extent, in unrelated organs (20). One of the most common cancers associated with DM is carcinoma of the colon (16, 18, 24). According to some authors, therapy for the malignancy has a beneficial effect on DM (1, 8, 11, 25, 26). However, other studies, as in the case of our patient, were not able to confirm this impression (6, 27).

About 15% of adults with DM have been found to develop a tumoral lesion (3, 18, 28) which may precede, coincide, or postdate the onset of the connective tissue disease (8, 16, 22, 29, 30). Meningioma also has a frequency of 15% among the various intracranial tumors affecting the population (31). However, despite the fact that the statistical incidence of a wide range of space occupying lesions coexisting with DM is similar to the prevalence of meningioma, the combination of DM with meningioma has not yet been described. The tumors reported in the literature with DM are carcinomas or other malignant neoplasms (1–30). The actual occurrence of meningioma with DM in our patient, who presented also a carcinoma of the colon, is unique.

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3 MU BTX-A into squares of 4 cm² at the axillary hyperhidrotic area, the effects of hyperhidrosis were observed within the follow-up period for up to 5 months.[5] The treatment of axillary hyperhidrosis with high-dose BTX-A seems to be as safe as low-dose BTX-A and has a lower rate of relapse.[9] The results of the present study were similar to those in other studies. BTX-A is a potent but very fragile toxin; therefore, care should be taken not to agitate the solution during the dilution and filling of the syringe. The different results of the duration effects of BTX-A with the same doses may be due to an inappropriate dilution method. The effects of BTX-A do not disappear completely at the end of 1 year. The optimal dose and the lowest dose for the treatment of axillary hyperhidrosis still needs to be defined to minimize dose-related side-effects, to lower the costs of treatment and to reduce the risk of antibody formation.[4,10]

Owing to the effects of factors such as temperature and emotional status on hyperhidrosis, an accurate evaluation about the effect of BTX-A on axillary hyperhidrosis may be rather difficult.

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Dermatomyositis without muscle weakness associated with transitional cell carcinoma of the bladder

To the Editor

A 63-year-old man presented with a 1-month history of skin eruptions on his face, chest and the extensor aspects of his elbows, hands and knees. He had no history of muscle weakness. Physical examination revealed heliotrope erythema, oedema of the upper eyelids, diffuse erythema and telangiectasia on his face and 'V' of the chest (fig. 1); there was violaceus erythema on the proximal interphalangeal joints, elbows and knees (Gottron's sign). The man presented no clinically detectable muscle weakness by manual strength test.

Laboratory investigations revealed normal complete blood count and biochemistry profile. Anti-streptolysin-O, C-reactive protein, rheumatoid factor, antinuclear antibody and anti-double-strand DNA were negative. Erythrocyte sedimentation rate was 24 mm/h. Creatine phosphokinase (CPK) level was

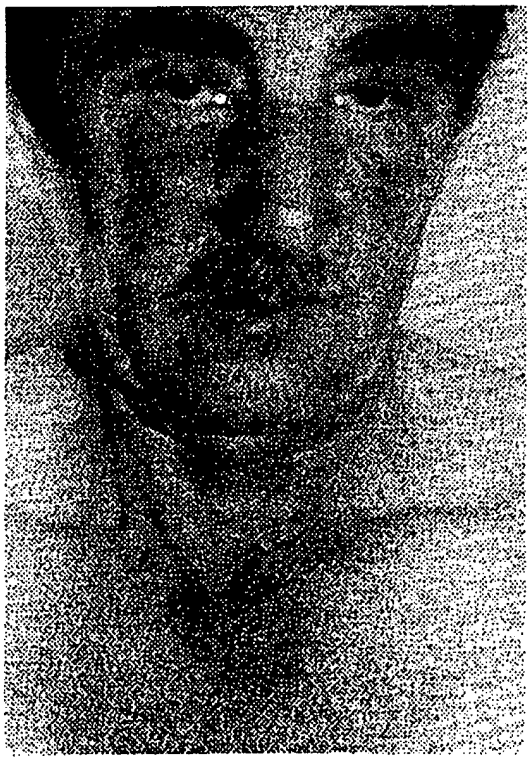

fig. 1 Erythema and oedema of the upper eyelids, diffuse erythema on the face and 'V' of the chest.

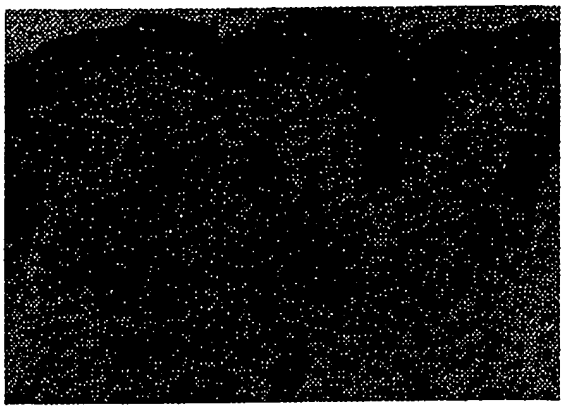

fig. 2. Histological picture of a skin specimen showing thinning of the epidermis, enlargement of blood vessels, and perivascular infiltrate of lymphocytes (haematoxylin and eosin, original magnification × 100).

44 U/L (normal 24–195) and aldolase 5 U/L (normal 3.1–7.6). A biopsy specimen was obtained from the lesion on the face. The findings of the histopathological examination were consistent with dermatomyositis (DM), showing thinning of the epidermis, hyperkeratosis, hydropic degeneration of the basal cell layer, and perivascular lymphocytic infiltrate in the dermis. There was homogeneous eosinophilic fibrinoid deposition along the dermoepidermal junction (fig. 2). Histopathological examination of the specimen obtained from the deltoid muscle was consistent with inflammatory myositis, but the findings of electromyography (EMG) and the serum levels of CPK and aldolase were normal.

Based on these clinical and laboratory findings the case was diagnosed as DM without muscle weakness, and systemic corticosteroid therapy (1 mg/kg daily) was initiated. Two months after beginning therapy, the man began to experience abdominal pain and fever. Haematuria and pyuria were detected. Abdominal ultrasound revealed hydronephrosis, in particular in the left kidney, and intravenous pyelography and cystoscopy evidenced a mass in the bladder. This mass was identified histopathologically as transitional cell carcinoma and was treated by surgery. The skin lesions revealed slight improvement with systemic corticosteroid therapy, but this treatment was tapered gradually before the surgery. The diagnosis was confirmed as DM without muscle weakness since no clinical or laboratory findings characteristic of myositis were detected throughout the follow-up period for 3 years; the man was prescribed sunscreens to protect the skin lesions during the follow-up period.

DM is characterized by cutaneous findings and inflammatory myositis. Characteristic cutaneous lesions of DM include a violaceous or heliotrope periorbital eruption or oedema, periungual telangiectasia, poikiloderma, photosensitivity, Gottron's papules and Gottron's sign. Cutaneous lesions may often precede clinical myositis and muscle weakness develops 3–6 months later in most patients. However, in some patients, muscle disease does not develop or appears to be minor or transient.[1–3] Therefore, the term 'amyopathic DM' (ADM), as described by Euwer and Sontheimer, is used to refer to patients who have classical cutaneous findings without clinical or enzymatic evidence of muscle disease for at least 2 years.[1] Cosnes *et al.*[2] designated their cases as DM without muscle weakness. However, controversy still exists concerning the definition of muscle disease. Those subjects who do not have overt muscle weakness or abnormal laboratory parameters are sometimes considered to be ADM.[1–3] On the contrary, some authors believe that the presence of minimal muscle involvement is inconsistent with the diagnosis of ADM.[4,5] Moreover, there is debate about the necessity of further investigations, such as EMG and in particular muscle biopsy, in cases where there is no overt muscle weakness. These diagnostic investigations are aggressive, and some authors emphasize that EMG and muscle biopsy are less sensitive than muscle enzyme studies for the detection of muscle disease.[1,6] We diagnosed our case as DM without muscle weakness because the man had no clinical and laboratory findings regarding muscle involvement except for the muscle biopsy.

There is still no consensus about the treatment of ADM. Some authors administer systemic corticosteroids to prevent the development of muscle weakness;[1] others avoid systemic corticosteroids, suggesting that ADM should be treated with antimalarial therapy instead because the adverse effects of corticosteroids must be balanced against the benign course of the disease and the rash of DM can be refractory to systemic corticosteroid therapy.[2,3] We prescribed corticosteroid therapy to prevent the development of muscle weakness, but we stopped the treatment 2 months later because of the onset of bladder carcinoma. We did not detect muscle weakness during the therapy, and the man's skin lesions did not improve markedly; moreover, the skin lesions persisted after the treatment of the cancer.

There have been reports of cases of ADM associated with an underlying malignancy, including lymphoma,[7] carcinoma of the lung, ovary, uterus,[8] breast,[2,6,7] colon,[4] kidney[7] and nasopharynx.[9] Bladder carcinoma is less frequently encountered in association with DM,[10] and to the best of our knowledge, the association of DM without muscle weakness, and transitional cell carcinoma of the bladder has not been reported previously.

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fig. 1 Brown violaceous annular plaques on the forehead.

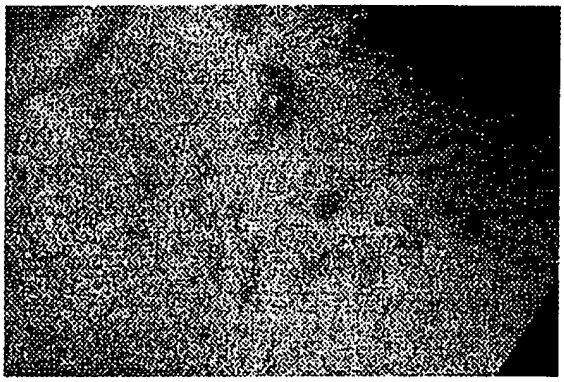

fig. 2 Lichenoid papules on the neck.

Lichen planus actinicus treated with acitretin and topical corticosteroids

To the Editor

Lichen planus actinicus, which is also known as lichen planus tropicus,[1] lichen planus subtropicus,[2] lichenoid melanodermatitis,[3] and lichen planus atrophicus annularis,[4] is a distinct variant of lichen planus, affecting mainly children and young adults. The majority of reported cases are from the Middle East, but cases from the Netherlands,[5] Italy,[6] Tunisia,[7] India,[8] East Africa,[3] the United States[4,9] and other countries have also been described. Clinically, four types of lichen planus actinicus can be distinguished: annular, plaque-like, dyschromic, and pigmented. The most common form is the annular type, which consists of erythematous brownish plaques with an annular configuration. In the plaque-like type, the lesions have a depressed brownish centre and an erythematous elevated border, sometimes resembling granuloma annulare. The dyschromic type presents as discrete and confluent whitish angular papules. Finally, the pigmented type consists of hypermelanotic patches, sometimes assuming a melasma-like appearance.[6,10]

A 51-year-old Tunisian patient presented with a 2-year history of asymptomatic skin lesions on his face, neck, and hands. The dermatosis started in summer and improved markedly during winter, but relapsed during the next sunny season. There was no prior injury or inflammation in these areas. The patient had no history of any contact with or intake of any drugs either.

Clinical examination revealed numerous brown violaceous annular plaques located on the forehead (fig. 1), lateral parts of the neck (fig. 2), and dorsal aspect of the hands. These lesions had a tendency to coalesce, forming circinate plaques. Some lichenoid papules on the neck could also be observed (fig. 2). The remaining parts of the skin and the mucous membranes were normal, and the nails were not affected.

A biopsy specimen was obtained from a representative lesion on the forehead. Microscopic examination revealed epidermal parakeratosis and coarse vacuolar degeneration of the basal cell layer. Dyskeratotic cells were noted. A band-like predominantly lymphocytic infiltrate with a few histiocytes in the papillary dermis was present. There was also marked pigmentary incontinence. Pigment was found in macrophages and as large extracellular clumps.

Immunofluorescence studies showed deposits of IgM and fibrin on necrotic keratinocytes. Routine laboratory investiga-

cannot conclude that irritation is an absolute requisite. It should be noted that for psoriasis, irritation is not necessary for anthralin to work. In fact, irritation may worsen psoriasis. Morhenn et al[11] have shown that anthralin is an immunomodulator by inhibiting a Langerhans cell–mediated immune response. Irritation is not a necessity for anthralin to display this immunomodulatory capability. There are also citations in the literature that skin irritants are not effective in the treatment of AA.[12,13]

I believe there are sufficient data to support efficacy for topical minoxidil solution and anthralin cream in the treatment of *patchy* AA.

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Dermatomyositis associated with ovarian transitional cell carcinoma

To the Editor: A 48-year-old woman presented with acute, pruritic edema and erythema of the eyelids and painful abdominal muscles. Three weeks after onset the patient was referred to our department.

Clinical examination revealed edema and a heliotrope coloration of the eyelids and the periorbital tissues, and an erythematous and maculopapular rash of the neck, chest, shoulders, and elbows. Small, purple, lichenoid papules were evident over the dorsal finger joints and the nailfolds were telangiectatic, edematous, hyperkeratotic, and tender.

During hospitalization diffuse and severe muscle weakness and pain appeared, especially in the proximal limb, neck, and abdominal muscles, leading to immobilization in bed. Moreover, the patient suffered from dysphonia and severe dysphagia, which required parenteral nutrition. The patient was treated with methylprednisolone (80 mg/d).

Laboratory examination revealed elevations in the levels of creatinine phosphokinase (4285 IU/L; normal value, ≤ 195 IU/L), circulating immune complexes (18.5 μg/mL; normal value, ≤ 5.0 μg/mL), cancer antigen 125 (181 IU/L; normal value, ≤ 35 IU/L), and soluble interleukin 2 receptors (1694 IU/mL; normal value, ≤ 100 IU/mL). Electromyography showed signs of acute myopathy, but no signs of denervation. Biopsy findings of the deltoid muscle showed no abnormalities. Pelvic ultrasound and total body computed tomographic (CT) scan demonstrated an irregularly shaped cystic mass (5 × 7 cm) in the left portion of the pelvis.

A tumor of the left ovary was diagnosed during laparotomy and a total hysteroadnexectomy as well as a partial omentectomy were performed. Histologic examination revealed a grade III transitional cell carcinoma of the left ovary with metastasis to the omentum (stage III) (Fig 1). A benign Brenner tumor was present in the right ovary.

Findings of a biopsy of the rectus abdominis muscle, performed during the operation, revealed numerous necrotic, hyalinized muscle fibers and some regenerated, atrophic, hypertrophic, and vacuolated muscle fibers with endomysial and perimysial fibrosis (Fig 2). Alkaline phosphatase reaction showed accentuated endomysial capillary loss. Interstitial edema and macrophage/T lymphocyte perivascular infiltrates were also present.

About 2 weeks after operation an almost full recovery of muscle function and partial improvement of the cutaneous features were observed. Corticosteroids were discontinued and treatment with high-dose intravenous immunoglobulins (400

Fig 1. Ovarian transitional cell carcinoma. Papillary fronds lined by layers of epithelium protrude into cystic spaces. (Hematoxylin-eosin stain.)

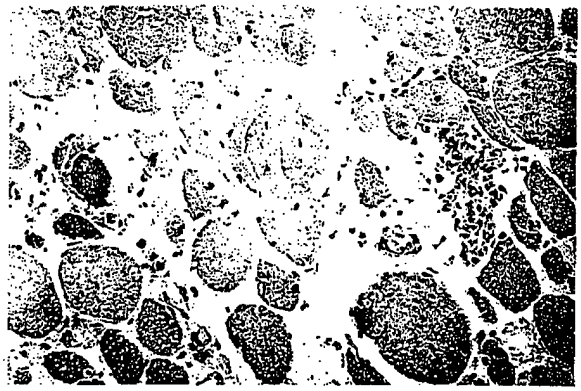

Fig 2. Necrotic, hyalinized, atrophic, hypertrophic, and vacuolized muscle fibers with endomysial and perimysial fibrosis. (Hematoxylin-eosin stain.)

mg/kg per day for 5 consecutive days) was started, with further clinical improvement. Moreover, the patient underwent a chemotherapy protocol with cyclophosphamide, cisplatin, and epirubicin. Within a month all elevated preoperative serum values decreased to normal levels. At present, 36 months after the operation, the patient is free from relapse, and serum cancer antigen 125 level, total body CT scan, and pelvic ultrasound do not reveal recurrence of the tumor.

Our case of dermatomyositis presented with rapid-onset severe muscle weakness, which led to immobilization, dysphagia, and dysphonia, with histologic features of an unusual acute necrotizing myositis. Remarkably, a substantial improvement of both muscle and cutaneous signs were observed in a few weeks after tumor debulking. In our case, the fast resolution of dermatomyositis after operation indicates a close relationship with cancer.

The malignancy found most in female patients with dermatomyositis is ovarian cancer.[1,2] The ages of patients who have dermatomyositis associated with ovarian malignancy range from the fifth to the seventh decades.[3,4] The stage of the tumor at diagnosis is typically III or IV, and the histologic subtype is serous carcinoma.[3]

The rare epithelial ovarian Brenner tumors constitute between 1% and 2% of all ovarian neoplasms and are classified in benign, borderline, malignant, and the extremely rare transitional cell carcinoma.[5] The latter term has been proposed for those primary ovarian carcinomas in which definite urothelial features are present, but in which no benign, metaplastic, and/or proliferating Brenner tumor can be identified.[6] The transitional cell carcinoma represents urothelial differentiation, and two subtypes have been described: papillary and malignant Brenner-like.[6,7] On gross examination, the tumors are solid, solid-cystic, or less frequently cystic.[6] The ovarian transitional cell carcinoma is rarely bilateral; however, contralateral benign Brenner tumors have been reported.[8] Transitional cell carcinoma is an aggressive neoplasm, often presenting with advanced stage disease, but appears to respond better to chemotherapy than other high-grade ovarian carcinomas.[6,9]

To our knowledge, our case represents the first association of dermatomyositis with an ovarian transitional cell carcinoma.

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Generalized basaloid follicular hamartoma syndrome

To the Editor: We were intrigued by the recent article by Wheeler et al[1] describing a new genodermatosis termed *generalized basaloid follicular hamartoma syndrome* (GBFHS). The authors describe 18 members of a family manifesting multiple milia; multiple comedone-like, dermatosis papulosa nigra–like, acrochordon-like, and other follicular lesions; hypotrichosis; tiny palmar "pits" probably involving sweat gland pores; and mild hypotrichosis. The skin manifestations were present at birth or early infancy, but tended to become static or even regress during adolescence.

We had a similar patient who presented at 3 years of age with hundreds of congenital milia, comedone-like and acrochordon-like lesions over the face (Fig 1, *A*), trunk (Fig 1, *B*), and extremities and short, sparse hair with an increased hair shaft diameter (112 μm; range, 50-90 μm). A biopsy specimen of an acrochordon-like lesion on the trunk taken to rule out basal cell carcinoma revealed trichoepithelioma. The child had no palmar pits and no known personal or family history of basal cell carcinoma. However, both his mother and maternal grandfather were born with similar skin lesions and hypotrichosis, which resolved during adolescence.

We too experienced similar difficulty establishing a diagnosis for our patient and considered the syndromes of Bazex-Dupre-Christol syndrome, which had overlapping but distinct features from our patient. However, we found 3 other reports, more similar to our case and the family described by Wheeler et al, which deserve mention.

In 1992, Oley, Sharpe, and Chenevix-Trench[2] described a syndrome featuring coarse sparse scalp hair and multiple milia on the face and limbs that spontaneously disappeared by adolescence. Basal

Fig 1. Hundreds of milia, comedone-like, and acrochordon-like lesions over the face **(A)** and trunk **(B)**.

cell carcinomas developed in the third and fourth decades of life. Similarly, Rapelanoro, Taieb, and Lacombe[3] described a patient with coarse, sparse hair and multiple milia on the face, limbs, chest, back, and pubic regions that disappeared in adult life; these patients did not have hypertelorism, increased sweating, or basal cell carcinomas. However, a follow-up report by these same authors was later published, in which additional family members were examined and found to have phenotypically variable features of the Bazex-Dupre-Christol syndrome, including basal cell carcinomas. Similarly, Andreani et al[4] recently reported a similar family with overlapping intrafamilial features between congenital hypotrichosis and milia ("Oley's syndrome") and the Bazex syndrome and suggested that these two entities were variants of the same condition. Again, the development of multiple basal cell carcinomas was a feature.

The disease reported in our family, Bazex-Dupre-Christol syndrome, and those previously described likely represent contiguous gene syndromes or different allelic forms of the same gene mutation, of which

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DERMATOMYOSITIS ASSOCIATED WITH TESTICULAR GERM CELL CANCER

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Dermatomyositis is occasionally associated with cancer of the breast, lung, stomach, colon, rectum and ovary.[1] We report a case of dermatomyositis and nonseminomatous germ cell tumors in which the former heralded progression of the latter.

CASE REPORT

A 31-year-old white man presented with symptoms of weakness and difficulty swallowing. Relevant history included right orchiectomy for nonseminomatous germ cell tumors (embryonal cancer) 3 years previously. Retroperitoneal lymph node dissection had not been performed nor was chemotherapy administered. Physical examination revealed overt proximal muscle weakness, obvious dysphagia, periorbital edema and cutaneous rash with scaling and dusky red patches (Gottron's sign). β-Human chorionic gonadotropin was 2,272 μg./l., creatine kinase 1,860 IU/l. (normal 24 to 204) and lactic acid dehydrogenase 840 IU/l. (normal 210 to 420). Pelvic and thoracoabdominal computerized tomography did not demonstrate metastases.

Diagnosis was stage III nonseminomatous germ cell tumor with associated dermatomyositis. A standard chemotherapeutic PEI regimen (20 mg./m^2 cisplatin, 100 mg./m^2 etoposide and 1,200 mg./m^2 ifosfamide) administered in 5-day courses for 4 cycles produced an almost dramatic amelioration of symptoms and a rapid decrease in serum levels. At 3-year followup the patient was symptom-free with a normal chemical evaluation.

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DISCUSSION

Although dermatomyositis remains primarily idiopathic in the majority of patients, there are reports of its association with various solid tumors and lymphoproliferative disorders.[1] A comprehensive 20-year followup of 392 patients with dermatomyositis indicated an increased risk of cancer in male and female patients.[1] Nevertheless, few patients have dermatomyositis associated with germ cell cancer. A literature search revealed 3 case reports of testicular germ cell tumor,[2,3] including a mediastinal germ cell tumor in 1[2] and teratoma in 2.[2] In our patient dermatomyositis appeared 3 years after excision of a primary nonseminomatous germ cell tumor and presumably signaled either an increased progression rate or relapse of the disease. A standard chemotherapeutic regimen provided a gratifying clinical response.

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Idiopathic Inflammatory Myopathy: Autoantibody Update

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Several defined, specific autoantibodies have been associated with polymyositis and dermatomyositis. These include autoantibodies to at least six of the aminoacyl-transfer-ribonucleic-acid synthetases, to the signal recognition particle, to the protein complexes labeled Mi-2 and PM-Scl, and several autoantibodies, such as anti-U1nRNP and anti-Ro/SSA, that have recognized associations with other conditions. These autoantibodies are a continuing area of interest. Recent studies have involved the clinical implications of these autoantibodies, and their potential significance for etiology and pathogenesis of the disease. This report will review recent studies of myositis autoantibodies and their clinical associations, both extramuscular features, such as interstitial lung disease and aspects of the myositis itself. New myositis autoantibodies continue to emerge, which may have clinical utility. Several have been associated with dermatomyositis, including juvenile dermatomyositis, which has a low frequency of traditional myositis autoantibodies. There is also new information regarding the antigenic targets of anti-Mi-2 and anti-PM-Scl, two of the earliest recognized myositis autoantibodies. New evidence over the past few years has challenged old concepts of the relationship of autoantibodies to the pathogenesis of myositis, and has suggested potential new mechanisms for the origin of the associated autoantibodies. Despite this progress, the reason for production of the autoantibodies and their role in tissue injury remain unknown.

Introduction

Screening tests, such as indirect immunofluorescence, Ouchterlony immunodiffusion, or protein A-assisted immunoprecipitation (IPP), shows that autoantibodies to nuclear or cytoplasmic antigens occur in a high proportion of patients with polymyositis (PM) and dermatomyositis (DM). Approximately 80% to 90% of patients with PM and DM have autoantibodies when combinations of tests are used. Inclusion body myositis (IBM) has shown a modestly higher frequency of positive anti-nuclear antibody tests than the general population, approximately 20% [1]. Such screening tests can direct attention toward autoimmune disease in patients with myopathies, but are of reduced clinical utility as a result of their lack of disease specificity and the frequency of positives in the normal population. Several autoantibodies to specific nuclear or cytoplasmic antigens have been associated with PM and DM and have been studied in detail. Most of these occur in only a relatively small percentage of patients with myositis. Together, established, defined autoantibodies occur in only about 50% of patients with myositis. These may nevertheless have more clinical significance, because of their disease specificity. Progress is being made in defining additional autoantibodies and narrowing this gap.

The association of autoantibodies to specific cellular antigens with some cases of autoimmune myositis has been recognized since the 1970s, with the description of myositis overlap syndromes with anti-nuclear-ribonucleoprotein (nRNP) and the identification of anti-Mi and anti-PM-1 (now anti-PM-Scl). Since then, studies have demonstrated several important concepts about defined myositis autoantibodies. Myositis autoantibodies have been divided into "myositis-specific autoantibodies" (MSAs) and "myositis-associated autoantibodies" (MAAs). MSAs occur almost exclusively in patients who have myositis at some point in their disease, while MAAs can occur in myositis but also often occur in patients without myositis. Myositis autoantibodies are usually present from the earliest stages of observed disease (with rare exceptions), and they usually persist over time even when disease is controlled or in remission, although the titer may change and they occasionally disappear [2–4].

The most common established MSA is anti-Jo-1, present in approximately 20% of patients with myositis in most studies [1,5]. Anti-Jo-1 reacts with histidyl-transfer-ribonucleic-acid [-tRNA] synthetase (hisRS), which catalyzes the binding of histidine to its tRNA ($tRNA^{his}$) [6]. Other autoantibodies react with aminoacyl-tRNA synthetases for threonine (PL-7), alanine (PL-12), isoleucine (OJ), glycine (EJ), and asparagine (KS), which bind those amino acids to their tRNAs [7]. These are much less frequent than anti-Jo-1, each present in less than 1% to 3% of patients with myositis. Generally patients react only with a

single aminoacyl-tRNA synthetase antigen, with rare exceptions [8]. Other MSAs include antibody to the signal recognition particle (anti-SRP), seen in 4% of patients myositis [9], and anti-Mi-2 in 5% to 10% [10]. MAAs are often associated with overlap syndromes. Anti-PM-Scl, for example, is associated with an overlap syndrome of myositis and scleroderma [11]. Other MAAs include anti-U1RNP, anti-Ro/SSA (both anti-Ro60 and anti-Ro52 [12]), and anti-Ku [13].

Myositis Autoantibodies and Their Clinical Associations

New studies of the occurrence of myositis autoantibodies

Recent studies have confirmed many of the general trends regarding the frequency of the traditional myositis autoantibodies and their subgroup associations that had previously been observed. However, some studies have suggested that the antibodies may not be as specific as they appeared. Among the most significant recent studies was that of Brouwer *et al.* [14••], who tested European patients with myositis for MSAs and MAAs. This study was distinctive not only in the size of its study population, with 417 total patients, but also in the sophisticated methods employed to detect the autoantibodies, including dot-blots using anti-sense RNA probes, and a new recombinant enzyme-linked immunosorbent assay (ELISA) for anti-Mi-2. ELISAs were also used to study antibodies to the 100 kd and the 75 kd proteins of PM-Scl, and Ro60 and Ro52. They found defined autoantibodies in 56% of patients, confirming the general impression that defined autoantibodies were found in about half of patients with idiopathic inflammatory myopathies (IIM) [1,5]. MSAs were found in 38% [14], with a similar proportion of MSAs in PM (38%) and in DM (41%), consistent with previous findings [1].

MSAs are usually found to be very rare in IBM. Love *et al.* [1] found defined autoantibodies in 12% of patients with IBM, all with anti-Ro/SSA (8% with anti-La/SSB), and none with MSAs. Brouwer *et al.* [14••] found a higher than expected frequency of defined autoantibodies (32%) and MSAs (18%) in IBM, including three anti-synthetases, one anti-SRP, and three anti-Mi-2. One previous study [15] had also reported anti-Jo-1 in IBM. The significance of the anti-Mi-2 found by Brouwer *et al.* [14••] in IBM is uncertain as a result of the lack of previous studies to establish the disease specificity of the new ELISA, which can detect anti-Mi-2 autoantibodies in patients who were negative with previous techniques [16].

The occurrence of anti-synthetases in IBM is surprising, because IBM differs clinically and histologically from the myositis usually associated with anti-synthetases, and patients with IBM do not usually show the extramuscular anti-synthetase syndrome [1,17]. Hengstman *et al.* [18•] described a patient with biopsy proven IBM and a consistent clinical presentation, whose serum had anti-Jo-1 detected by multiple techniques. Of interest is that the patient responded to prednisone treatment with marked improvement in strength, a response expected more with anti-Jo-1-associated PM than with IBM. This single case cannot exclude co-existence of diseases, but it indicates that the antibody may carry clinical significance even if IBM is seen by biopsy. If further studies confirm these observations, it may even point to potential etiologic or pathogenetic relationships between some cases of IBM and PM. The authors have not detected MSAs as part of IBM, and the authors consider them very rare. If traditional autoantibody tests in IBM reveal confirmed MSAs, the diagnosis should be reviewed.

Anti-synthetases

Specific MSAs have been associated with particular clinical features and syndromes. The best studied of these is the syndrome associated with anti-Jo-1 and other anti-synthetases [1,17]. Numerous studies have documented the high frequency of myositis in patients with anti-Jo-1, and the very low frequency of anti-Jo-1 in connective tissue disease patients without myositis [6,19]. However, case reports and some series have shown that a small percentage of anti-Jo-1 patients do not have myositis during their observed course. The frequency of myositis in studies can depend on how sera were chosen for testing and other factors, but is usually over 90% for anti-Jo-1, at some point in the course [17]. Some non-Jo-1 anti-synthetases have had a lower frequency of myositis. In a recent preliminary report studying anti-synthetases in Japanese patients [20], 100% of 25 anti-Jo-1 patients had myositis, but it was seen in only 13% of those with anti-PL-12, questioning its designation as an "MSA." Myositis is more common in US and UK anti-PL-12 patients [17,21] but is less frequent than in anti-Jo-1 patients [5,22]. The most recently described anti-synthetase, anti-KS, has also been associated with a lower frequency of myositis in the small number of patients studied [20,23•].

The anti-synthetase syndrome is characterized by several extramuscular manifestations. Interstitial lung disease is the most important because of its clinical impact and effects on mortality [1]. It occurs in 50% to 80% of anti-synthetase patients. It can range in severity and course from asymptomatic to fulminant acute respiratory distress syndrome [24–27]. In a recent retrospective analysis of interstitial lung disease in patients with PM and DM seen over a 9-year period by Douglas *et al.* [28•], the most common pattern in those with biopsies was that of non-specific interstitial pneumonia (NSIP) (81.8%). However, less than one third of patients were biopsied, which may have introduced a selection bias. The prognosis was better than for idiopathic pulmonary fibrosis (more often usual interstitial pneumonia), and was similar to that of NSIP in other settings. Anti-Jo-1was found in 38% of those tested, a lower frequency than in some previous studies. Anti-Jo-1 patients had a similar prognosis to that of the overall group, but the histology in anti-Jo-1 patients was not

specified. There have been numerous case reports of bronchiolitis obliterans organizing pneumonia (BOOP) in association with anti-Jo-1 or other anti-synthetases [29]. This pattern also has a relatively good prognosis and responsiveness compared with idiopathic disease.

Arthritis is also more common in the anti-synthetase syndrome than in others with PM or DM, observed in 50% to 90% of patients. It is sometimes deforming [30] but usually non-erosive, although erosive arthritis can occur [31••]. Other extramuscular features are considered to be part of the syndrome. Love *et al.* [1] found Raynaud's phenomenon in 60%, and mechanic's hands in 70%. Mechanic's hands, a hyperkeratotic rash along the edges of the fingers, was found in only 17% by Schmidt *et al.* [31••]. It can occur in association with other autoantibodies and, like other features of the syndrome, is not specific for anti-synthetase patients. Some, but not all, studies have also found an increased frequency of Sjögren's syndrome and sclerodactyly [17,31••]. Other features have been observed in anti-synthetase patients in low frequency in these studies, but it is unknown if they are part of the syndrome or occurred incidentally. The DM rash is usually found in a minority of anti-Jo-1 patients, but the rash was more frequent with other anti-synthetases [4].

In a recent extensive review of anti-Jo-1 clinical associations, Schmidt *et al.* [31••] noted that for most patients in their series and in the literature, the first symptom was not from the myositis, but from an extramuscular feature. Most of their patients did have signs of myositis at diagnosis, but they also saw patients with anti-Jo-1 who did not develop myositis, including a small number who did not have interstitial lung disease either. Most of these had a compatible arthritis, another common and often prominent feature of the syndrome. Myositis could be suppressed by treatment of other features, but this does not seem to explain all cases. These findings provide further support for the impression that anti-synthetase autoantibodies are more specific for the "anti-synthetase syndrome," which may not be fully expressed, than for myositis itself [22]. They also suggest that testing for these antibodies may be helpful in evaluating patients with interstitial lung disease, and some patients with arthritis (such as those with negative rheumatoid factor or non-erosive disease), even if myositis is not evident.

Original studies indicated that anti-Jo-1 patient sera reacted with the histidyl-tRNA synthetase enzyme but not the tRNA for histidine ($tRNA^{his}$) [6]. This was also true for patient sera with antibodies to other aminoacyl-tRNA synthetases with the exception of anti-PL-12 sera [21], which almost all reacted with alanyl-tRNA synthetase and $tRNA^{ala}$. However, in a more recent study [32] about one third of anti-Jo-1 sera reacted with a conformational epitope of $tRNA^{his}$. Further study is needed to determine if there is any additional clinical significance to the presence of anti-$tRNA^{his}$ autoantibodies, beyond that conferred by anti-Jo-1.

Other myositis-specific autoantibodies

The signal recognition particle is a ribonucleoprotein complex containing six proteins (of molecular weights 72, 68, 54, 19, 14, and 9 kd) and an RNA labeled 7SL. Early studies indicated that the 54 kd protein was the major antigen for most patients [9], but subsequent studies have indicated that the 72 kd protein is also an important antigen [33]. No clinical differences have yet been found between patients recognizing different components. The antibody can be detected by immunoprecipitation of the complex and identification of the 7SL RNA [9,14••], but the autoantibodies do not react directly with the 7SL RNA.

In the original studies, almost all patients with anti-SRP had PM. Although the total number of patients with this antibody has been described as small, many have had incomplete response to treatment or a need for continuing treatment with immunosuppressive agents, or acute and severe disease [9,33]. In one study [1], the mortality was higher than in other antibody-defined groups. That study also found a higher frequency of cardiac involvement. In a recent preliminary report, Hengstman *et al.* [34] also found incomplete responses and a need for continuing treatment, but were unable to confirm the higher frequency of cardiac involvement.

Brouwer *et al.* [14••] studied anti-SRP in myositis using a dot-blot with antisense RNA to identify 7SL in immunoprecipitates. Although the majority of anti-SRP patients (14 of 20 patients) had PM, more patients with DM were found than in previous studies (5 of 20). This was probably caused by the sensitive antibody detection method, but diagnostic criteria or population differences may have contributed. The occurrence of anti-SRP outside of PM has significance for assessing its potential etiologic and pathogenetic implications, as discussed in this report.

Anti-Mi-2 autoantibodies have had very high myositis specificity, and most patients (90%–95%) have had the DM rash. It is found in 10% to 20% of patients with DM in most studies [1,10] but may be more frequent in some ethnic groups or geographic locations [35]. It has been seen in children and adults with DM [36], and the subgroup with anti-Mi-2 has not been clinically distinguishable from other patients with DM.

Brouwer *et al.* [14••] found anti-Mi-2 outside the usual associated clinical group more frequently than expected. Their new anti-Mi-2 ELISA, using four overlapping recombinant fragments that span the length of the Mi-2β protein, found anti-Mi-2 in 58 patients, of which 17 (29%) had PM (9% of PM). There appeared to be differences in epitope reactivity between patients with PM and DM, as judged by the frequency of sera reacting with the different antigen fragments, but there was overlap between PM and DM. Previously, an ELISA using a single fragment (similar to "NM") was extensively tested for reaction with autoimmune sera, and it had the expected DM specificity, similar to other tests [37]. The epitopes were not localized further. Ge *et al.* [38] had previously found that a conformational

epitope reacted with all anti-Mi-2 sera that were positive by immunoprecipitation and immunodiffusion, but it is unknown whether this epitope was expressed in the recombinant ELISA.

False-positive results could have contributed because only eight of 17 ELISA-positive PM patient sera were confirmed by Western blotting. Studying anti-Jo-1, Schmidt *et al.* [31••] noted that low-level positive ELISA tests without confirmatory blotting were often not associated with the expected clinical manifestations. However, Brouwer *et al.* [14••] did not note differences in the levels of anti-Mi-2 in PM and DM sera. The increased sensitivity of antibody detection also resulted in an increase in the coexistence of MSAs, which are usually mutually exclusive. The myositis specificity of the new ELISA requires further testing, but if equal to that of other anti-Mi-2 tests, then the ELISA would be a valuable addition in view of its increased sensitivity. It is clear that in interpretation of autoantibody tests clinically, it is important to consider the technique used for detection.

Anti-Mi-2 was originally identified by immunodiffusion (anti-Mi-1 was a different precipitin line made by the prototype serum that proved to be unrelated) and showed a nuclear pattern by indirect immunofluorescence. By immunoprecipitation, anti-Mi-2 sera showed a series of proteins, the strongest of which migrated at 240 kd, and represented the major antigen. Two forms of the protein were identified, labeled anti-Mi-2α and anti-Mi-2β [39], which are 75% identical and react with anti-Mi-2 sera. The protein sequences contain a series of motifs, including a DEAH box, that indicate a role as a helicase and zinc finger motifs of the "PHD" type [37]. Mi-2α and Mi-2β were officially designated "CHD4" and "CHD3" based on the presence of a "chromo" domain, a "helicase" domain, and a "DNA-binding" domain [40]. These characteristics suggested a role in chromosomally-mediated regulation of transcription. This has since been demonstrated more directly. Mi-2β was shown to be part of a multi-subunit protein complex labeled "nucleosome remodelling deacetylase" (NuRD) [41]. This complex also contains histone deacetylases, which modify chromatin by affecting histone binding to DNA. Mi-2 modifies chromatin by an active, ATP-dependent mechanism. Thus NuRD can modify chromatin by at least two different mechanisms. In a recent study [42•], recombinant Mi-2 was shown to have nucleosome remodelling activity. The NuRD complex may also have a role in gene regulation through DNA methylation [43]. In the past few years, evidence has suggested a role for Mi-2 in transcriptional regulation in several cellular processes and has been the subject of significant scientific interest.

Anti-PM-Scl has been considered a MAA because some patients have scleroderma without myositis, and most patients have an overlap syndrome with features of the two conditions ("scleromyositis") [11,44]. However, unlike MAAs, anti-PM-Scl is mutually exclusive with other MSAs, and myositis is seen in the majority of patients (75%) [11]. Arthritis is also common, as is the DM rash, but there is usually limited cutaneous scleroderma. The myositis tends to be relatively responsive to treatment [13].

The antibody reacts with a complex of at least 11 proteins whose cellular role had previously been unknown. The major antigenic components of PM-Scl are the 100 kd protein, which reacts with most sera, and the 75 kd protein, which reacts with about half of sera [14••]. The reactive epitopes have been extensively characterized [45,46•].

Sequencing and analysis of these proteins eventually led to the recognition that the PM-Scl complex was the human homologue of the "exosome" that had been identified in yeast [47••,48•]. The complex is composed of exoribonucleases [49•] and is involved in RNA processing and degradation. Patient sera show nuclear and nucleolar staining by indirect immunofluorescence, but the complex was also found in the cytoplasm.

Significance of myositis-specific autoantibodies

Such studies raise the issue of whether antibody-defined subgroups represent distinct diseases, with aspects of etiology or pathogenesis that differ from patients with antibody-negative PM or DM, or represent a response in some patients to a more general process that can also occur in the absence of antibodies. This relates to the question of whether the antibodies are involved in pathogenesis, but the antibodies could alternatively be markers of another process. Studies in the past few years have provided interesting new information relevant to these issues.

Mozaffar and Pestronk [50••] compared the muscle histopathology of 11 patients with anti-Jo-1 with that of other patients with PM and DM. Although only three patients were considered to have a skin rash, all 11 showed perifascicular atrophy, usually associated with DM. In DM, this is accompanied by a vasculopathy and capillary loss, with reduced capillary index (here 0.55), but the capillary index in the anti-Jo-1 patients was not significantly reduced (0.88) compared with the patients with PM (0.95). The anti-Jo-1 patients all showed perimysical connective tissue fragmentation, a finding that was uncommon in PM and DM, but was also seen in all of their patients with fasciitis. This suggests a fundamental difference in the pathogenetic mechanisms of myositis in the anti-Jo-1-defined group, favoring a distinct condition. Preliminary studies have also suggested distinctive features of muscle histology in anti-SRP-associated myositis [33], with some patients showing necrosis without inflammation.

A contrary impression derives from the report of Nagaraju *et al.* [51••], describing an interesting mouse model of myositis, based on observations that major histocompatibility complex Class 1 molecules are abnormally overexpressed on muscle fibers in myositis. Transgenic mice were developed in which expression of MHC Class I molecules on muscle could be controlled by addition or removal of tetracycline. When MHC expression was

induced, the mice developed progressive weakness over several months, with elevation of creatine kinase and histologic myositis. Eight of 23 transgenic mice with myositis developed anti-Jo-1 antibodies. There was no difference in disease expression noted between mice with antibody positive and antibody-negative myositis mice. In this model, anti-Jo-1 production appeared to be a secondary event, that was not required for, or evidently contributing to, development of myositis. Anti-Jo-1 arose in myositis without a specific stimulus for reaction to Jo-1 protein, arguing against molecular mimicry with a virus, a hypothesis that had been previously suggested. However, it is unknown whether human anti- Jo-1 arises in the same manner.

An alternative to the molecular mimicry hypothesis as an explanation for autoantibodies is the hypothesis that they result from events occurring in the process of apoptosis [52••]. Proteins undergoing proteolytic cleavage during apoptosis may generate fragments with new epitopes, which may be presented on the cell surface in apoptotic blebs. Of particular interest was a report by Casciola-Rosen *et al.* [52••] that analyzes numerous cellular autoantigens associated with connective tissue diseases for cleavage by granzyme B, as could occur during cytotoxic lymphocyte granule-induced apoptosis. They found that autoantigens were much more likely than other proteins to be cleaved by granzyme B, seen with 80% of autoantigens, and this would account for cleavage of some autoantigens that are not cleaved by caspases. Myositis autoantigens were prominent among those which are cleaved, although there were exceptions.

New Antibodies

Newly identified antibodies

Myositis-specific autoantibodies can be helpful in establishing a diagnosis if present, but they are not useful in excluding a diagnosis because approximately half of patients with myositis do not have any of the established, defined autoantibodies. As noted, screening tests suggest the presence of additional antibodies, and there is interest in determining these additional specificities. In the past few years, several newly-defined autoantibodies with apparent myositis association have been identified, and established antibodies have been noted to have new myositis associations.

It was recently found that some patients with myositis react with human PMS-1, a DNA mismatch repair enzyme that is a member of the MutL family [53•]. The autoantibody was detected by immunoprecipitation of S35-labeled PMS-1, but patient autoantibody did not react by immunoblot. The antibody recognized the C-terminal fragment, the portion that varies in different MutL-family enzymes. Antibody was found in sera of 7.5% of 53 patients with myositis but not in sera from any of 94 patients with lupus or scleroderma or 39 normal subjects, although it was found in a patient with active herpes zoster. All four anti-PMS-1 myositis sera reacted with at least one other autoantibody, including one that also had anti-Mi-2. One anti-PMS-1 serum also had antibodies to other MutL family mismatch repair enzymes, PMS-2 and MLH-1. Anti-PMS-2 was also found in a second myositis serum, which also had anti-MLH-1, and in one lupus serum. Anti-MLH-1 alone was found in one myositis serum. The finding of patients with myositis independently reacting with different members of a related family of enzymes is reminiscent of the aminoacyl-tRNA synthetases, except that autoantibodies to more than one of these repair enzymes co-exist in the same individuals, and thus far no distinctive syndrome or clinical associations have emerged.

Two other new autoantibodies with an apparently strong myositis association have been described in recent preliminary reports. Both were identified by immunoprecipitation from human cultured cell extracts, and both appear to be predominantly associated with DM, including juvenile DM. Overall, children with myositis have a lower frequency of myositis autoantibodies, in part caused by the much lower frequency of anti-Jo-1 autoantibody compared with adults. In a preliminary study of the autoantibodies in 47 children with IIM, anti-PM-Scl was the most frequently encountered autoantibody, seen in 10 patients; anti-Mi-2 was seen in four, but anti-Jo-1 in only two patients [54]. However, five patients had a new autoantibody labeled anti-MJ. Further study in a wider population found the antibody in 14 patients (17.5%), including 13 with DM (more in juvenile than adult patients) and one with systemic-lupus-erythematosus–myositis overlap [55]. Seven had relatively severe disease, and eight had calcinosis. Anti-MJ autoantibody reacts with an unidentified protein of approximately 140 kd.

A second new autoantibody was later found in 31 patients, 29 of whom had DM, including 20 children and nine adults [56]. This was approximately 14% of those tested, but the autoantibody was more frequent in amyopathic dermatomyositis. Among these patients, with a characteristic DM rash for an extended period without development of clinically evident myositis, the authors have seen the anti-155kd antibody in approximately 80%, while MSAs and MAAs have been less frequent than in usual DM [57]. Some of the sera with anti-155kd autoantibodies have had an associated antibody reacting with a 95 kd protein labeled Se. The cellular role of the new antigens (MJ, 155kd, and Se) has not yet been determined, and it is unknown whether these apparently nuclear proteins have any functional relationship to PMS-1, Mi-2, or other known antigens. The presence of the new antibodies in some cases of adult and juvenile DM suggests that juvenile DM is not a separate condition distinct from adult DM, which has been suggested in the past based on the higher frequency of calcinosis and intestinal perforation.

One previously described antinuclear autoantibody, anti-56kd, has been an exception to generalizations about the established myositis autoantibodies. In the original

studies, sera from the majority of patients in all myositis clinical subgroups reacted with an unidentified 56 kd component of nuclear ribonucleoproteins by Western blot [58,59]. The antibody was relatively specific for myositis, with few exceptions. It was most common in juvenile DM (92%), but was even common in myositis with malignancy (75%) [60]. The titer seemed to vary with disease activity, which suggests the possibility of a role in pathogenesis. Of particular interest is a recent preliminary report confirming the frequent occurrence of this antibody in juvenile DM, although not quite as high a rate (62%) [61]. This difference may have related to population differences, because it was more common in association with DQA1*0501. The fact that the antibody has been found in such a high proportion of highly disparate clinical subgroups raises the possibility that it is a secondary response, such as a cross-reaction with a muscle protein. However, given the observed disease frequency and specificity, it would have potential clinical utility regardless of its role in disease. Alternatively, anti-56 kd may be related to the newer DM antibodies such as anti-MJ and anti-155kd, and may together account for many of the positive anti-nuclear antibodies, and have important implications for the disease.

New myositis associations

A recent report found that a previously described antibody to a tRNA-related protein antigen (Wa), that was found in scleroderma, can occur in myositis as well [62]. Of interest was that the two patients with anti-Wa had interstitial lung disease, suggesting a clinical similarity to patients with anti-synthetases. It has previously been suggested that the association of myositis with antibodies to tRNA-related antigens may extend further than the anti-synthetases alone. Antibodies to Fer (believed to be elongation factor 1α) and Mas [1,14••] immunoprecipitate tRNA and occur in myositis, but they are not myositis-specific [63]. Myositis antibodies to cytoplasmic antigens not associated with tRNA have also been noted (anti-KJ [5], anti-SRP), and the reason is still not understood. The cellular role of Wa antigen is unknown.

Several other autoantibodies that occur in myositis, but whose primary association is with other conditions, have been studied recently. In findings confirming those of a previous study in another population, Tormey *et al.* [64•] found that 54% of patients with scleroderma and anti-U3RNP (anti-fibrillarin) and diffuse cutaneous involvement had associated muscle involvement considerably higher than expected. Pulmonary hypertension is also increased in this group.

Rutjes *et al.* [12] had previously demonstrated an increase in anti-Ro52 in patients with myositis (20%), that was even stronger among patients with anti-Jo-1 (58%). The authors found a similar high frequency of anti-Ro52 in non-Jo-1 anti-synthetase patients [65] and in 47% of anti-PM-Scl patients. Anti-Ro52, at 25%, was the most common defined autoantibody in European patients with myositis [14••], compared with only 4% with anti-Ro60.

Anti-endothelial cell antibodies were recently found in 38% of patients with IIM [66]. They were found in two of three patients with interstitial lung disease, independent of anti-synthetases. Anti-histones were also recently found in patients with IIM, noted in 17%, predominantly reacting with histone H1 [67]. Antibodies to 20S proteasomes, cytoplasmic complexes involved in protein degradation, are common in myositis (63%), reacting with the αC9 component [68]. They are also common in systemic lupus erytemetosus (58%) and primary Sjögren's syndrome (39%) but not in rheumatoid arthritis or normals, suggesting a potentially meaningful, but not myositis-specific, response [69].

Conclusions

Myositis-related autoantibodies can be identified in an increasing proportion of patients with PM and DM. They can be helpful in diagnosis caused by their disease specificity, and in further characterization of a patient's disease caused by their clinical subgroup associations. It may be useful to consider MSAs as an additional criterion in the Bohan and Peter criteria set, as described in this report.

Major questions remain regarding these antibodies. The reasons for production of MSAs, for disease and subgroup specificity, and for the localization of tissue injury, are unknown. The reason autoantibodies to different anti-synthetases in different patients are associated with similar clinical syndromes is not understood. Finally, it is unknown if MSAs play a role in pathogenesis.

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☐ **1:** NP_060268. YTH domain family...[gi:31377750]

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AUTHORS Ota,T., Suzuki,Y., Nishikawa,T., Otsuki,T., Sugiyama,T., Irie,R., Wakamatsu,A., Hayashi,K., Sato,H., Nagai,K., Kimura,K., Makita,H., Sekine,M., Obayashi,M., Nishi,T., Shibahara,T., Tanaka,T., Ishii,S., Yamamoto,J., Saito,K., Kawai,Y., Isono,Y., Nakamura,Y., Nagahari,K., Murakami,K., Yasuda,T., Iwayanagi,T., Wagatsuma,M., Shiratori,A., Sudo,H., Hosoiri,T., Kaku,Y., Kodaira,H., Kondo,H., Sugawara,M., Takahashi,M., Kanda,K., Yokoi,T., Furuya,T., Kikkawa,E., Omura,Y., Abe,K., Kamihara,K., Katsuta,N., Sato,K., Tanikawa,M., Yamazaki,M., Ninomiya,K., Ishibashi,T., Yamashita,H., Murakawa,K., Fujimori,K., Tanai,H., Kimata,M., Watanabe,M., Hiraoka,S., Chiba,Y., Ishida,S., Ono,Y., Takiguchi,S., Watanabe,S., Yosida,M., Hotuta,T., Kusano,J., Kanehori,K., Takahashi-Fujii,A., Hara,H., Tanase,T.O., Nomura,Y., Togiya,S., Komai,F., Hara,R., Takeuchi,K., Arita,M., Imose,N., Musashino,K., Yuuki,H., Oshima,A., Sasaki,N., Aotsuka,S., Yoshikawa,Y., Matsunawa,H., Ichihara,T., Shiohata,N., Sano,S., Moriya,S., Momiyama,H., Satoh,N., Takami,S., Terashima,Y., Suzuki,O., Nakagawa,S., Senoh,A., Mizoguchi,H., Goto,Y., Shimizu,F., Wakebe,H., Hishigaki,H., Watanabe,T., Sugiyama,A., Takemoto,M., Kawakami,B., Yamazaki,M., Watanabe,K., Kumagai,A., Itakura,S., Fukuzumi,Y., Fujimori,Y., Komiyama,M., Tashiro,H., Tanigami,A., Fujiwara,T., Ono,T., Yamada,K., Fujii,Y., Ozaki,K., Hirao,M., Ohmori,Y., Kawabata,A., Hikiji,T., Kobatake,N., Inagaki,H., Ikema,Y., Okamoto,S., Okitani,R., Kawakami,T., Noguchi,S., Itoh,T., Shigeta,K., Senba,T., Matsumura,K., Nakajima,Y., Mizuno,T., Morinaga,M., Sasaki,M., Togashi,T., Oyama,M., Hata,H., Watanabe,M., Komatsu,T., Mizushima-Sugano,J., Satoh,T., Shirai,Y., Takahashi,Y., Nakagawa,K., Okumura,K., Nagase,T., Nomura,N., Kikuchi,H., Masuho,Y., Yamashita,R., Nakai,K., Yada,T., Nakamura,Y., Ohara,O., Isogai,T. and Sugano,S.
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JOURNAL Nat. Genet. 36 (1), 40-45 (2004)
PUBMED 14702039
COMMENT PROVISIONAL REFSEQ: This record has not yet been subject to final NCBI review. The reference sequence was derived from BC050284.1.
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Summary
The recent structural studies have narrowed down the number of possible models for sister chromatid cohesion and provide a clearer view of how the components of the cohesin complex interact. Nonetheless, several key questions regarding the mechanism of sister chromatid cohesion still need to be addressed: can cohesins form higher-order structures, how is the cohesin complex recruited to specific regions of the chromosome, how does the passage of the replication fork lead to the linkage of sister chromatids and what role does ATP hydrolysis play in sister chromatid cohesion. Undoubtedly, the establishment and maintenance of sister chromatid cohesin is a dynamic process and many of its moving parts still need to be elucidated.

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Protein Sequence Motif

YTH: a new domain in nuclear proteins

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A novel 100–150-residue domain has been identified in the human splicing factor YT521-B and its *Drosophila* and yeast homologues. Homology searches show that the domain is typical for the eukaryotes and is particularly abundant in plants. It is predicted to adopt a mixed α-helix–β-sheet fold and to bind to RNA. We propose the name YTH (for YT521-B homology) for the domain.

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One of the most prominent features of eukaryotic genes is their discontinuity. Analysis of the working draft of the human genome has shown that, on average, introns account for 95% of the pre-mRNA [1]. The precise removal of intron sequences by the spliceosome is crucial for gene expression. However, the sequences of the two splice sites and the branch point that are recognized by spliceosome components are clearly insufficient to identify the exons in the pre-mRNA sequence. Correct recognition of exons is achieved by the cooperative action of multiple splicing factors auxiliary to the spliceosome [2]. These factors bind in a sequence-specific manner to the pre-mRNA [3,4] and recruit the spliceosome components to the splice sites. The nuclear protein YT521 has been identified in two-hybrid screens with splicing factors [5,6]. It interacts with several splicing factors, both in two-hybrid and co-immunoprecipitation assays [5,6]. In addition, the alternative splicing patterns of the splicing factor SRp20 and hTra2-β pre-mRNAs are altered by YT521-B [6]. YT521 does not belong to any of the known splicing factor families. The only sequence feature that it shares with some of the splicing factors is an RE/D repeat. Here we report the identification of a new domain in splicing factor YT521-B and a number of proteins of unknown function that could be involved in RNA binding.

Domain characterization

During BLAST searches to identify YT521-B homologues, a conserved part of the protein was identified between residues 356 and 499 of the rat YT521-B

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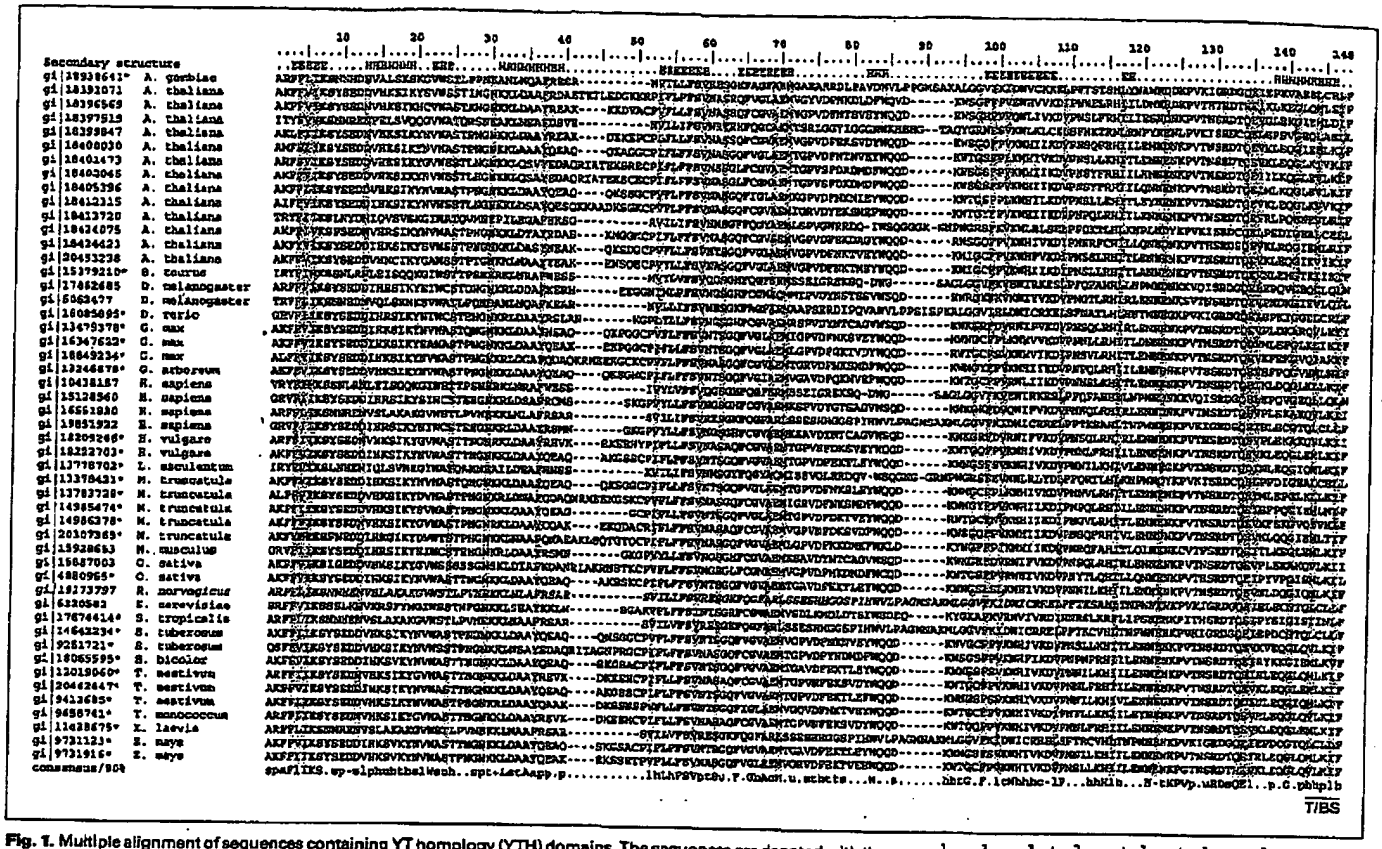

Fig. 1. Multiple alignment of sequences containing YT homology (YTH) domains. The sequences are denoted with the GeneBank identifier of the corresponding nucleotide sequence followed by the species name. The GeneBank identifier for the *Saccharomyces cerevisiae* refers to protein entry in the database. Translations of partial EST sequences are indicated with an asterisk. The sequences were identified using searches of the translated EST and the nonredundant nucleotide databases at NCBI using rat YT521-B (shown in italic). Wherever available, the conceptual translation provided in the database was used for the alignment. If no conceptual translation was provided (i.e. for the EST sequences), the reading frame identified by the BLAST search was used if it did not contain stop codons or unknown residues. Redundant sequences originating from the same species were omitted. The similar residues that are present in all sequences are shaded (green) using the PAM250 matrix. The identical residues are shaded in yellow. The secondary structure, as predicted by the PHD program, is shown on top. E denotes extended (β-strands) structure and H denotes the predicted α-helices. The multiple sequence alignment (accession number ALIGN_000432) has been deposited at the European Bioinformatics Institute (ftp://ftp.ebi.ac.uk/pub/databases/embl/align/).

protein. We therefore performed a PSI-BLAST [7] search with this portion of the YT521-B protein, using an exclusion threshold of 0.005. After four iterations, multiple proteins from *Arabidopsis thaliana*, *Oryza sativa*, *Homo sapiens*, *Mus musculus*, *Drosophila melanogaster*, *Plasmodium falciparum* and *Saccharomyces cerevisiae* where found to have similar regions, with E values in the range 10^{-11}–10^{-60}. Many of these protein sequences were derived from automated gene prediction and were not confirmed by mRNA or EST sequences. To identify sequences of existing proteins, we performed BLAST [7] searches with the conserved region against the translated nonredundant nucleotide database at NCBI (filtered using 'biomol_mrna[PROP]' as a keyword) and the translated EST database.

The sequences from these searches that aligned to the full length of the query and had an E value $<10^{-6}$ were aligned using CLUSTALW [8] after the redundancies had been removed (Fig. 1). Additional BLAST searches against the genome databases confirmed that the conserved region is present exclusively in eukaryotic genomes.

The conserved region appears to define a new domain in these proteins, which we termed the YT homology (YTH) domain. The YTH domain is usually located in the middle of the protein sequence. The domain shows remarkable conservation across a wide species range, with 14 invariant and 19 highly conserved residues. The proteins present in the alignment do not share significant similarity outside the YTH domain, with the exception of the closely related vertebrate homologues of YT521.

We used SMART [9,10] to search the SMART and PFAM databases for additional known domains in the proteins that contain YTH. The search failed to identify any known domains except for three C–C–C–H-type zinc finger domains in GI:18397519, an *A. thaliana* predicted protein of unknown function. Therefore, we conclude that the YTH domain defines a new protein family.

The putative secondary structure was determined using the PHD program [11]. The domain is predicted to have a mixed αβ-fold, with four α-helices and six β-strands. The conservation pattern follows the predicted secondary structure, with three blocks of conserved sequence separated by loops of variable size. Notable features of the domain are the highly conserved aromatic residues located in the β-sheet.

Most of the proteins identified in the BLAST searches are of plant origin, with 13 distinct sequences coming from a single species (*A. thaliana*). It is unclear whether this protein family is more widespread in plants or whether the observed species distribution is because of bias in the databases.

Predicted function

Biochemically and functionally, YT521-B has been extensively characterized as a pre-mRNA splicing factor [6,12]. In contrast to the other known splicing factors, it lacks a recognizable domain that can confer RNA binding. The conservation of aromatic residues in the β-sheets of the YTH domain is similar to the RNA recognition motif (RRM) domain. In the RRM domain conserved aromatic residues located in the β-sheet are crucial for RNA binding [13]. In addition, experimental evidence shows that the YTH domain is not involved in protein–protein interactions [6]. Based on this, we predict that the biological function of the YTH domain is to bind to RNA.

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BLUF: a novel FAD-binding domain involved in sensory transduction in microorganisms

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A novel FAD-binding domain, BLUF, exemplified by the N-terminus of the AppA protein from *Rhodobacter sphaeroides*, is present in various proteins, primarily from Bacteria. The BLUF domain is involved in sensing blue-light (and possibly redox) using FAD and is similar to the flavin-binding PAS domains and cryptochromes. The predicted secondary structure reveals that the BLUF domain is a novel FAD-binding fold.

The prototype and identification of the BLUF domain

AppA is a multidomain protein from the phototrophic proteobacterium *Rhodobacter sphaeroides* (accession number L42555). The N-terminus of the AppA protein is involved in the regulation of photosynthesis gene expression, although its mechanism of action is not well understood [1–4]. The N-terminus of the AppA protein was identified as being involved in repression of photosynthesis genes by blue-light [1], and Gomelsky and Kaplan showed that the N-terminal ~120 residues bind flavin adenine dinucleotide (FAD) noncovalently with an apparent 1:1 stoichiometry [4]. At the time of publication of Ref. [4], two additional bacterial proteins showing sequence similarity to the N-terminus of AppA had been identified [4]. One of these, YcgF from *Escherichia coli* (also known as F403 and b1163; accession number P75990), has been purified and shown to bind FAD [4].

Using the region most conserved between AppA and YcgF (residues 16–108 of AppA), we performed a BLAST search of the nonredundant protein database and a TBLASTN search of the microbial genome database at NCBI, as well as a TBLASTN search of the individual unfinished microbial genomes at the sequencing centers listed in our Acknowledgements. Our searches revealed a variety of uncharacterized proteins containing domains with significant similarity to the N-terminus of AppA. We designated these domains BLUF, for 'sensors of blue-light using FAD'. Most of these proteins are from two branches of Bacteria, Proteobacteria and Cyanobacteria (Fig. 1). Bacterial genomes contain up to three BLUF domains per genome. No BLUF domains are encoded by the currently available genomes of Archaea. Four BLUF domains are found in Eukarya, all from the unicellular flagellate *Euglena gracilis* [5] (Fig. 1).

Involvement of the BLUF domain in sensory transduction

To our knowledge, the functions of only two proteins containing BLUF domains have been tested experimentally. Similar to the BLUF domain in *R. sphaeroides* AppA, the BLUF domains from the recently described photoactivated adenylyl cyclase (PAC) from *E. gracilis* are also involved in the blue-light-dependent control of enzyme activity. Two BLUF domains belong to the α-subunit of the enzyme, PACα, and two to the PACβ subunit [5] (Fig. 1). To gain an insight into the putative role of the BLUF domains in other proteins we analyzed their domain architecture using the SMART [6] and Pfam [7] databases. Based on the deduced domain structures, all

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Humoral Immunity in Polymyositis/Dermatomyositis

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Autoantibodies are found in most patients with polymyositis (PM) or dermatomyositis (DM) and 35–40% of these patients have myositis-specific antibodies. Twenty-five to thirty percent have anti-aminoacyl-tRNA synthetases, of which anti-Jo-1, directed at histidyl-tRNA synthetase, is by far the most common. Patients with anti-synthetases have a high frequency of myositis, interstitial lung disease, Raynaud's phenomenon, and other features constituting an "anti-synthetase syndrome." Anti-synthetases tend to react with conformational epitopes and to inhibit enzymatic activity, suggesting reaction with conserved regions. Sera with antibodies to alanyl-tRNA synthetase (anti-PL-12) also have antibodies to $tRNA^{ala}$, whereas most sera with other anti-synthetases do not react directly with tRNA. Production of the antibodies appears to be antigen-driven, and is influenced by HLA genes, although an initiating factor, possibly a viral infection, may be important. Antibodies to other cytoplasmic antigens, most notably the signal recognition particle (anti-SRP), are seen in a small percentage of patients. Patients with anti-SRP do not tend to develop the anti-synthetase syndrome, but may have very severe disease. Antibodies to the nuclear antigen Mi-2 are also specific for myositis, and are strongly associated with DM. Several autoantibodies, including anti-PM-Scl, anti-Ku, and anti-U1 and U2 RNP, have been associated with scleroderma-PM overlap.

The role of humoral immunity in the myositis of PM and DM has not yet been clarified. Capillary loss and ischemic damage are important in DM, and seem to be mediated by humoral mechanisms, whereas cell-mediated attack on muscle fibers is important in PM. The mechanism of skin injury in cutaneous lesions is not known, but antibody deposition is inconsistent and uncommon.

Whether the myositis-specific antibodies are involved in disease pathogenesis is not yet known, although there is no direct evidence for this. An understanding of the reasons for production of these antibodies, however, should provide insight into the etiology and pathogenesis of PM and DM.
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Polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory myopathies characterized by weakness and elevated muscle enzymes [1]. Patients with DM have associated characteristic cutaneous manifestations. The cause of these conditions is unknown, but there is ample evidence of the involvement of autoimmunity in the myopathy [2]. Two lines of evidence have been pursued in recent years that have greatly enhanced our understanding of the autoimmune response in PM/DM. These include studies that have defined and characterized the disease-specific autoantibodies in sera of myositis patients, and studies characterizing the inflammatory infiltrates in myositis muscle [3].

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Abbreviations:
alaRS: alanyl-tRNA synthetase
anti-synthetase: antibodies to aminoacyl-tRNA synthetase
DM: dermatomyositis
glyRS: glycyl-tRNA synthetase
hisRS: histidyl-tRNA synthetase
HLA: human leukocyte antigen
ILD: interstitial lung disease
ileRS: isoleucyl-tRNA synthetase
K: killer
MSA: myositis-specific antibodies
NK: natural killer
PM: polymyositis
RNP: ribonucleoprotein
SLE: systemic lupus erythematosus
SRP: signal recognition particle
thrRS: threonyl-tRNA synthetase
tRNA: transfer ribonucleic acid

HUMORAL VERSUS CELLULAR IMMUNITY IN MYOSITIS

There is increasing knowledge about the mechanism for muscle damage, although there is less specific information about the underlying mechanisms of cutaneous and other extra-muscle manifestations. The operative processes in muscle damage may differ between PM and DM [4]. Cell-mediated immunity appears to be a very important pathogenic mechanism in PM, whereas humorally mediated damage to muscle blood vessels seems to be more important in juvenile and adult DM. However, humoral autoimmunity in the form of autoantibodies is prominent in both conditions.

Arahata and Engel found that muscle biopsies from patients with adult PM show many fibers that are surrounded and invaded by mononuclear cells [5,6]. These fibers are intact, and therefore this cellular attack seems to be a primary event, rather than a response to necrosis. Phenotypic analysis of the cells that are surrounding and invading muscle fibers indicates that most are T lymphocytes and many of them express CD8. The proportion of CD8+ cells is higher among invading than surrounding cells. Other markers demonstrate that these surrounding and invading cells are cytotoxic rather than suppressor cells [7], with little involvement of killer (K) or natural killer (NK) cells. These are strong indications that a T-cell-mediated, antigen-directed attack on muscle occurs in PM and plays a major role in muscle cell damage. Similar findings are seen in inclusion body myositis, another form of idiopathic inflammatory myopathy.

A higher percentage of B cells is seen in DM. Very few

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surrounded and invaded fibers are seen in DM, even fewer than are seen in Duchenne's muscular dystrophy [6]. This suggests that cell-mediated immunity is not a major factor in DM, whereas other evidence supports a major role for humoral immunity in DM. In many cases of adult DM and almost all cases of juvenile DM, there is prominent evidence of involvement of muscle blood vessels, with capillary loss and ischemic muscle damage [1,4]. Endothelial cell abnormalities have frequently been observed. Endothelial injury and capillary loss occur early in disease, and have been demonstrated in biopsies from patients with DM prior to other changes on light microscopy and prior to weakness [8].

Other evidence of vascular involvement in DM has been found. Nailfold capillary abnormalities may be seen in DM, including bushy capillaries, giant capillary loops, and other changes [9]. The pattern of perifascicular atrophy of muscle fibers associated with PM/DM, attributed to ischemic effects, is more common in DM than PM, and especially common in juvenile DM. Inflammatory infiltrates often are concentrated in the interstitial and perivascular areas [5].

The vessel injury in DM appears to be complement-mediated. Deposition of the membrane attack complex of complement is consistently seen in the muscle blood vessels in juvenile DM [10]. Such deposition is seen in adult DM as well, in almost 90% of cases in a recent study [8], but it has not been reported in PM. Although this indicates that complement is activated locally, it does not necessarily imply that it is a primary event that plays a pathogenic role. However, Emslie-Smith and Engel [8] reported that the deposition of membrane attack complex is a very early finding in DM muscle and may occur prior to other observed abnormalities on the muscle biopsy, which is consistent with a primary role in muscle injury. They noted that in one case a patient who had not yet become weak and whose muscle biopsy was normal by light microscopy showed unusually extensive membrane attack complex deposition in muscle vessels. The patient went on to develop overwhelming, fatal DM.

The factors leading to local complement activation are not entirely clear, because deposition of antibody in muscle vessels is not consistently observed [11]. However, several studies have reported deposition of IgG or IgM antibody in muscle vessels in at least some cases [12,13]. Consistent with the previous observations, deposition is observed more frequently in DM than in PM, and more frequently in juvenile than in adult DM. It is possible that antibody or immune complexes are able to activate complement locally either without deposition of antibody or with release of antibody, leading to the observations noted.

Despite these indications of a role for humoral immunity in the muscle injury of DM, its role in the development of the skin manifestations in DM is unclear. The similarities of the erythematous or poikilodermatous lesions of DM to lupus suggest a possible role for antibody. However, deposition of antibody in DM is inconsistent, and deposition along the dermal-epidermal junction as is seen in lupus is very uncommon [14].

AUTOANTIBODIES

Autoantibodies are an easily demonstrated and clear expression of autoimmunity in PM/DM (Table I). Reichlin and Arnett [15] were able to demonstrate autoantibodies to nuclear or cytoplasmic cellular antigens in almost 90% of PM/DM patients, indicating that they are very common. Autoantibodies of defined specificity are found in approximately 45–55% of adults and a small percentage of children. Others have autoantibodies detected by screening tests, such as indirect immunofluoresence, but are negative for recognized antibody specificities. Approximately 35–40% of PM/DM patients have "myositis-specific autoantibodies" (MSA) [16]. Almost all patients with MSA have myositis, either alone or as part of overlap syndromes. It is rare for an individual patient to have more than one MSA. Generally, particular MSA have been associated with characteristic clinical features, so that the MSA tend to mark clinical subgroups. One antibody, anti-56 kD, is an exception to these rules, having been reported in a high percentage of all patients, including a high percentage of children [17]. About 25% of PM/DM patients has defined autoantibodies that are not MSA, antibodies that have been associated with other connective tissue diseases, such as anti-U1RNP or anti-Ro/SSA. These antibodies may occur alone or in association with any of the MSA.

Any possible role of these antibodies in disease pathogenesis remains speculative, even in patients whose muscle injury appears to be humorally mediated. There has been no evidence that it is the MSA that locally activate complement in DM resulting in vessel damage. In fact, the MSA are least common in juvenile DM, the condition in which the evidence is strongest for the importance of a humorally mediated vasculopathy. However, a pathogenetic role has not been excluded. The MSA are of great interest because of their potential value as clues to cause as well as their possible use in diagnosis and patient classification.

ANTI-SYNTHETASES

The autoantibodies that are most common as a group and the best studied among the MSA are those that react with the aminoacyl-tRNA synthetases. These cytoplasmic enzymes catalyze the binding of an amino acid to its specific transfer RNA (tRNA) for transport to the ribosome and incorporation into a growing polypeptide chain during protein synthesis [18]. The most common anti-synthetase, anti-Jo-1, reacts with histidyl-tRNA synthetase (hisRS) [19,20]. Four other anti-synthetase autoantibodies have been identified, reacting with synthetases for threonine (thrRS), alanine (alaRS), glycine (glyRS), and isoleucine (ileRS) [21–23]. The relative frequencies of these four non-Jo-1 anti-synthetases vary in different studies, possibly reflecting differences among populations. Anti-Jo-1 appears to be about 5–10 times as common as any one of the four, and about 2–4 times as common as all four together.

Each of the 20 enzymes that performs this function for a particular amino acid must accurately recognize the specific tRNA for its amino acid to maintain fidelity of translation, thus requiring a "second genetic code" on the tRNA that is only now being deciphered [24]. Each enzyme is therefore different, distinctive on the molecular and the antigenic level. Each anti-synthetase recognizes only a single synthetase, and no serum has been reported to have more than one of the five anti-synthetases. This is remarkable considering the similarity of the five anti-synthetases in their clinical associations.

Clinical Picture Anti-synthetases have been found in both adult PM and adult DM, as well as in some patients with overlap syndromes that involve myositis. The presence of these biologic markers in both PM and DM suggests that at least some cases of PM and DM may have similar origins despite their apparent differences in pathogenesis. Among patients with anti-Jo-1, PM is 2–10 times more common than DM [25,26], but among patients with other anti-synthetases, PM is less predominant [27,28], and may be less frequent than DM [16]. DM was seen in five of six patients with anti-EJ (anti-glyRS) antibodies [29].

The myositis of patients with anti-synthetases is clinically similar to that of patients without the antibodies. However, recent studies have indicated that patients with anti-synthetases may respond less completely to treatment than others with myositis [16], and more often have recurrences as treatment is withdrawn.

Other features that have been associated with anti-synthetases make these patients distinctive enough among myositis patients to be designated as having an "anti-synthetase syndrome." The most distinguishing feature is the very high frequency of interstitial lung disease (ILD), found in at least 50–75% of those with anti-synthetases compared to 10–20% of others with myositis [26,27,30,31]. Although ILD can be asymptomatic, it also can be severe or fatal. Some patients with each of the anti-synthetases have had ILD as the predominant clinical problem, occasionally without evident associated myositis [27]. An increased frequency of arthritis (> 90%) and Raynaud's phenomenon (60%) has also been associated with anti-synthetases [16]. In patients with anti-synthetases, the arthritis may be more severe and may be deforming, a manifestation not usually seen in other myositis patients without overlap [32]. An interesting

Table I. Autoantibodies Associated with Polymyositis/Dermatomyositis

Antibody	Antigen	Antigen Structure	Detection[a]	Overall Frequency (%)	Clinical Subgroup	Clinical Features	Comments
Anti-synthetases							
Anti-Jo-1	Histidyl-tRNA synthetase	50 kD subunit dimer	IPP, ID, CIE, ELISA, AAI, IB	18	Adult PM > adult DM	ILD; arthritis; Raynaud's Phenom.; Mechanic's hands; flare on taper common	HLA DR3 in >90% of white patients[b]
Anti-PL-7	Threonyl-tRNA synthetase	80 kD subunit	IPP, ID, CIE, AAI	3	Adult DM, PM	Similar to anti-Jo-1	No reaction in IB
Anti-PL-12	Alanyl-tRNA synthetase + $tRNA^{ala}$	110 kD + tRNAs	IPP, CIE, AAI	3	Adult DM, PM, ILD	Similar to anti-Jo-1	Reacts with tRNA
Anti-OJ	Isoleucyl-tRNA synthetase	145 kD component of multi-enzyme synthetase complex	IPP, AAI	1	Adult DM, PM, ILD	Similar to anti-Jo-1	May react with certain other complex components
Anti-EJ	Glycyl-tRNA synthetase	75 kD	IPP, AAI, IB	1	Adult DM > PM	Similar to anti-Jo-1	
Other anti-cytoplasmic antibodies							
Anti-SRP	Signal recognition particle	54 kD component of particle	IPP, IB	4	Adult PM	Very severe, treatment-resistant disease may occur. Anti-synthetase features not increased.	Some sera react with other particle proteins; HLA DR5 may be increased
Anti-KJ	Unidentified translation factor	30, 34 kD	ID, IB	< 1	Adult PM	ILD, Raynaud's	Native protein may be 120 kD
Anti-Fer	Eukaryotic elongation factor 1α	48 kD	IPP	Very rare	Nodular myositis		Heterogeneous tRNA on IPP
Anti-Mas	Unidentified tRNA	4.5S tRNA	IPP	< 1	PM	Alcoholic rhabdomyolysis	
Autoantibodies in Scleroderma-Myositis Overlap							
Anti-PM-Scl	Nucleolar complex of 11–16 proteins	100 kD (> 90%) 75 kD (25% to 50%)	ID, IPP, IB	8–10	PM-SSc; PM; SSc	"Scleromyositis"	Strong association with HLA DR3
'Anti-U1RNP	U1 small nuclear RNP	70 kD	ID, IPP, IB	12	Overlap syndromes	Overlap with SLE or SSc is common	
Anti-U2RNP	U2 small nuclear RNP	B", A' U2 specific proteins	IPP, IB	1	PM-SSc	Most with overlap	Usually associated with anti-U1RNP
Anti-Ku	DNA-binding protein	80 kD + 70 kD heterodimer	IPP, IB	1	PM-SSc or other overlap syndromes; SLE; SSc		Relative species specificity
Dermatomyositis-specific antibodies							
Anti-Mi-2	Nuclear protein complex	240 kD? component of complex	ID, IPP, ELISA	5–10	Adult or juvenile DM	Classical cutaneous manifestations; no increase in anti-synthetase features	HLA DR7 associated
Other associated autoantibodies							
Anti-56 kD	Component of a nuclear ribonucleoprotein	56 kD	IB	87	All subgroups		Can be seen in SLE without myositis, usually in low titer
'Anti-Ro/SSA	RNA-protein complex	60 kD	ID, IPP, IB, ELISA	10	Overlap syndromes with SLE, Sjögren's		May be accompanied by anti-La/SSB

[a] ELISA, enzyme-linked immunoabsorbent assay; IPP, immunoprecipitation; ID, immunodiffusion; CIE, counter-immunoelectrophoresis; AAI, aminoacylation inhibition; IB, immunoblot.
[b] Goldstein *et al*, 1990.
[c] Most patients with these antibodies do not have myositis.

cutaneous feature is "mechanic's hands," which is marked by hyperkeratosis with fissuring and hyperpigmentation along the radial and palmar aspects of the fingers, appearing as dirty horizontal lines. First described in association with connective tissue diseases and Raynaud's phenomenon [33], it was recently found to be associated with anti-synthetases [16].

Immunologic Aspects The anti-synthetases have many interesting features. Almost every serum with any of the anti-synthetases inhibits the antigenic enzyme specifically, without affecting activity of other synthetases [19]. This inhibitory activity is proportional to the amount of antibody [25]. It is noteworthy because inhibition of the antigen is not consistently seen with animal antisera to these enzymes. Some animal antisera resulting from immunization with purified synthetases have specifically inhibited the antigenic enzyme whereas others have not [34–36]. The consistent inhibition by the autoantibodies suggests reactivity with active regions of the enzyme that tends to be highly conserved, areas usually spared when an animal is immunized with a protein from another species. Inhibition of the functional activity of the antigen is a characteristic observed with other autoantibodies tested, including the anti-mitochondrial antibodies of primary biliary cirrhosis, the antibodies to the U small nuclear ribonucleoproteins (RNPs) in lupus and overlap syndromes, and others.

In immunoprecipitation studies, a restricted pattern of tRNA is always found associated with the antigenic enzymes that is characteristic for the particular anti-synthetase. The tRNA immunoprecipitated by anti-Jo-1 (anti-hisRS) has been sequenced and identified as a tRNA specific for hisitidine ($tRNA^{his}$). The tRNA immunoprecipitated by anti-PL-12 (anti-alaRS) have also been found to be specific for the amino acid of the associated antigenic synthetase ($tRNA^{ala}$) [22,37,38], and this is presumed to be the case for the other anti-synthetases. In most cases, deproteinized tRNA is not antigenic, whereas the enzyme protein retains antigenicity despite removal of tRNA [21,23,37]. The enzyme has affinity for the tRNA, which at least partially explains its presence in the immunoprecipitate, but immunoprecipitation of tRNA is not necessarily an expected property of an antibody to a synthetase enzyme. Animal antisera to synthetases have generally not immunoprecipitated the cognate tRNA [21]. One implication of this is that the autoantibodies of PM/DM may specifically spare the tRNA binding site. This would be expected if the immunogen were the complex of synthetase and RNA, as would be predicted by some hypotheses of anti-synthetase development.

An exception to this pattern of restriction of antigenicity to the protein is anti-PL-12. Although most sera with antibodies to other synthetases (with some exceptions) do not react with deproteinized tRNA, most sera with anti-PL-12 have both antibodies to the synthetase and antibodies to tRNA for alanine ($tRNA^{ala}$), which can be separated from each other [22]. Anti-$tRNA^{ala}$ could represent an anti-idiotypic response to the anti-alaRS [22]. It has also been suggested that the anti-$tRNA^{ala}$ may have been the original antibody, possibly arising as an antibody to viral RNA, with anti-alaRS developing as an anti-idiotype against the anti-$tRNA^{ala}$ [22,39].

Anti-OJ (anti-ileRS) is of particular interest because, unlike the other anti-synthetases that react with free, individual cytoplasmic proteins, anti-OJ reacts with an enzyme that is a component of the multi-enzyme synthetase complex [23,40]. In higher eukaryotes, eight of the aminoacyl-tRNA synthetases are found complexed together, along with additional non-synthetase proteins. Anti-OJ immunoprecipitates this entire complex, but only a very limited set of tRNA [23]. At 150 kD, ileRS is the second largest complex component. Most sera with anti-OJ consistently and specifically inhibit ileRS activity almost completely, suggesting that despite immunoprecipitation of the entire complex, ileRS is the main antigen. Certain sera also show evidence of reactivity with other components of the complex (other synthetases) in addition to ileRS, including lysyl, glutaminyl, and/or leucyl-tRNA synthetases. These sera show the same tRNA immunoprecipitation pattern as other anti-OJ sera [40]. This is the only situation in which reaction of a single serum with more than one synthetase is seen, and it is restricted to other synthetases that are complexed to the main antigen.

The anti-synthetases appear to react primarily with conformational epitopes. This was demonstrated for anti-PL-7 (anti-thrRS) by showing that it does not react by immunoblot despite strong reactivity in immunoprecipitation [34]. In comparison, animal sera raised against thrRS react well by immunoblot. Although most anti-Jo-1 autoimmune sera react well by immunoblot, this may not represent reaction with strict linear epitopes. When tested systematically by epitope scanning against synthesized sequential hexapeptides of the entire Jo-1 amino acid sequence, no anti-Jo-1 sera reacted with any peptides, whereas animal antisera showed strong reactivity with peptides throughout the sequence [35]. Anti-OJ also does not usually react with ileRS in immunoblot [40]. Study of anti-Jo-1 epitopes using proteolytic hisRS fragments appears to indicate similar or shared epitopes recognized in immunoblot [41]. Further study using recombinant mutant forms of hisRS also indicates similarity in immunoblot epitopes, and some similarities in conformational epitopes recognized in immunoprecipitation [42]. The latter study also indicated that some differences between sera could be detected, and that sera reacted with multiple epitopes. This would be consistent with a scenario in which reaction with one epitope results from a common initiating event, followed by an expansion of the reaction against the antigenic molecule itself [43].

More direct evidence that the anti-Jo-1 response is antigen driven comes from recent studies of Miller *et al* [35]. In one case in which serial serum samples over time were available beginning prior to the development of anti-Jo-1, the antibody was observed to develop several months prior to the onset of myositis. Initial sera showed predominance of IgM, but in later samples IgM anti-Jo-1 fell and IgG titers rose, demonstrating an isotype switch that is typical of an immunization. In addition, antibody affinity for the Jo-1 antigen increased over this period. Affinity maturation toward the recognized antigen strongly suggests that that antigen is the target and is driving the response.

Even if the anti-Jo-1 response is antigen driven, the patient's hisRS is not necessarily the original immunogen. Because different anti-synthetases are targeted by different PM/DM patients with a similar syndrome, these antibodies pose the crucial question of why the synthetase enzymes were selected as antigens in this disease. An aspect of the synthetase function may be important. The anti-synthetases are directed at an enzyme family that shares an analogous function, but structural relatedness is limited. Some general similarities have been identified between sequences and structures of the bacterial forms of the enzymes that allow the separation of two general classes of synthetases [44], but no cross-reactivity with multiple synthetases is seen either by autoantibodies or animal antisera. This raises the possibility that the antigens were selected because of their function, suggesting that the antigens are the intended target.

The important features of synthetases leading to their antigenicity in myositis are not clear. Binding of tRNA by synthetases has been suggested as a possibly important factor leading to the development of these autoantibodies. Nucleic acid binding is a feature of several autoantigens in systemic autoimmune diseases, such as Ro/SSA, La/SSB, U1RNP and other small nuclear ribonucleoproteins, and others. The presence of the synthetases in the cytoplasm has also been suggested as a possibly important factor. Antibodies to cytoplasmic antigens are relatively common in myositis, being present in 21% of patients by indirect immunofluorescence [15]. There may be an association of myositis with antibodies to cytoplasmic antigens, or possibly antigens involved in protein synthesis [19,45]. It may be possible to get a clue to the important features of the antigens that initiate these responses by looking at other proteins that can be antigenic in myositis besides synthetases, particularly when features of the anti-synthetase syndrome are seen.

OTHER ANTI-CYTOPLASMIC ANTIBODIES

Autoantibodies to specific cytoplasmic proteins other than synthetases are found in a very small number of PM/DM patients, but a variety of such antibodies has been seen. The most important ap-

pears to be anti-signal recognition particle (SRP), which was estimated to occur in about 4% of PM/DM patients [46]. It reacts with the SRP, which consists of at least six proteins (72, 68, 54, 19, 14, and 9 kD) and a 7S RNA labeled 7SL. The SRP functions in the translocation of newly formed secretory or membrane proteins into the endoplasmic reticulum by binding to the signal sequence of the nascent polypeptide chain through its 54-kD protein. The 54-kD protein is the major antigen for autoantibodies as determined by immunoblotting studies, in which the 54-kD protein reacts with almost all anti-SRP sera, and immunoprecipitation, in which the 54-kD protein is usually the most prominent band. Some sera also react with the 68- and/or the 72-kD proteins, usually in addition to the 54 kD. Thus far, no sera have been found to react directly with the 7SL RNA, although as part of the particle, it is incorporated into the immunoprecipitate and helps identify the antibody.

Anti-SRP is strongly associated with PM. In our recent series, all 12 patients with the antibody had PM without the DM rash [46]. The clinical subgroup of PM patients that is marked by anti-SRP differs significantly from the group marked by anti-synthetases. The frequency of ILD has been much lower, at about 10%, comparable to PM patients without anti-synthetases. Arthritis and Raynaud's phenomenon are also uncommon. However, unlike PM patients without anti-SRP or anti-synthetases, many of the patients with anti-SRP had a very severe course and were very resistant to therapy [46]. The anti-SRP subgroup and other antibody-determined subgroups may have clearcut clinical differences from each other, and from PM/DM overall [16]. The antibodies can therefore be clinically useful in patient characterization and prognosis. These differences also suggest the possibility of significant differences in pathogenetic and/or etiologic factors.

As noted, immunoprecipitation of specific tRNA, a particular property of the autoantibodies, suggests that tRNA binding may be an important feature leading to immunogenicity of these proteins. Two autoantibodies that immunoprecipitate tRNA, but are not anti-synthetases, have been found in myositis: anti-Fer and anti-Mas [47]. Both occur in very low frequency (< 1%), but anti-Mas is more common than anti-Fer. Anti-Fer appears to react with eukaryotic elongation factor 1α [48], a 48-kD translation factor that has affinity for aminoacylated tRNA. The antibody immunoprecipitates heterogeneous tRNA that appears to contain all forms of tRNA, as might be expected because elongation factor 1α can bind to aminoacylated tRNA non-specifically. The antibody does not react in immunoblot, indicating exclusive reactivity with conformational epitope(s), but at least one epitope is highly conserved. This antibody has been found in only one patient with localized nodular myositis and has not been associated with the anti-synthetase syndrome. Anti-Mas immunoprecipitates a small RNA that appears to be a tRNA, but no associated protein has been found [47]. Among a large series of patients, two were found to have anti-Mas, and both were similar in their history of alcohol-related rhabdomyolysis prior to the development of PM, in their history of diabetes, and in their HLA type (DR4, DRw53) [16]. However, the anti-synthetase syndrome has not been found with anti-Mas. Also, it should be noted that antibodies to tRNA-related antigens may occur in other conditions, such as anti-Wa, which is associated with scleroderma [49], or antibody to initiator methionine tRNA, which has been associated with Sjögren's syndrome [50]. Thus, an association with tRNA may not be the common factor in development of these antibodies.

Although antibodies to tRNA-related proteins other than anti-synthetases have not been associated with the anti-synthetase syndrome, antibodies to a protein involved in protein synthesis and translation have been associated with a picture that does look like the anti-synthetase syndrome. Anti-KJ was found in two patients with PM, ILD, and Raynaud's phenomenon [45]. The antigen has not yet been identified, but it was determined to be a translation-related protein, because IgG from the two patients inhibited translation of globin messenger RNA *in vitro*. The antigen did not appear to be a tRNA-related protein because no tRNA was immunoprecipitated, nor was it a synthetase, because none was inhibited despite the inhibition of translation. Preliminary evidence indicates that there is at least one other antibody to a non-tRNA-related translation factor, in addition to anti-KJ, that can be associated with PM with ILD. Thus, a relationship to translation and protein synthesis may be an important factor in initiation of these responses.

Various hypotheses have been suggested to explain how these properties might lead a protein to become antigenic [2,51], particularly the possibility that viral RNA or protein might share similar features to the cellular proteins, with molecular mimicry leading to cross-reactive antibodies. An alternative scenario would be an interaction of viral RNA or protein with translation-related proteins (synthetases or factors) during the course of infection leading to immunogenic complexes. Picornaviruses such as Coxsackie, which have been implicated as possible initiating agents in myositis for other reasons [52], are RNA viruses with the potential for such interactions.

AUTOANTIBODIES IN SCLERODERMA-POLYMYOSITIS OVERLAP

Other autoantibodies are also important in PM/DM. Of particular interest are autoantibodies associated with scleroderma-polymyositis overlap. This combination is a fairly common form of overlap syndrome, and autoantibodies are very common in these patients [53]. Certain autoantibodies have been particularly associated with this overlap syndrome, although most can also be seen in the absence of overlap. The most common is anti-PM-Scl, which occurs in about 8% of all myositis patients in the U.S. [54], and about 3% of scleroderma patients [55]. Most patients with the antibody are adults, but it may occur in children. It can be seen in PM/DM or scleroderma without overlap, but overlap is seen in 50% or more of the patients with the antibody. Some overlap patients have myositis early in their course that responds to treatment, whereas scleroderma persists. Diffuse or limited cutaneous scleroderma may occur with this antibody. Blaszczyk and colleagues have reported that the scleroderma-myositis overlap syndrome that occurs with anti-PM-Scl can be distinguished from other forms of overlap, and have referred to it as "scleromyositis" [56,57]. Some of the features of systemic scleroderma were not seen, and it was felt to have a better prognosis.

Anti-PM-Scl reacts with an antigen in the nucleolus that may also be present in the nucleus. In indirect immunofluorescence, a pattern of intense nucleolar staining with significant nucleoplasmic staining is usually seen, although nucleolar staining alone was seen with affinity-purified anti-PM-Scl antibody [58]. Although PM/DM has been associated with antibodies to cytoplasmic antigens as described above, a high frequency and variety of anti-nucleolar antibodies have been associated with scleroderma. The fact that anti-PM-Scl is associated with scleroderma as well as myositis fits this pattern, and suggests a closer association with the scleroderma antibodies. The antigen appears to be a large complex of 11-16 proteins ranging from 20 kD to 110 kD, without known associated nucleic acid [59,60]. Sera of almost all patients with anti-PM-Scl react with a 100-kD protein, and about half also react with a 75-kD protein. The two proteins, which both appear to be part of the complex, are antigenically distinct and have no amino acid sequence homology [61,62]. This is another example of antibodies to more than one component of the same complex, suggesting an antigen-driven response, with the complex as antigen. No other component has yet been determined to be antigenic. The sequence of the 75-kD protein actually predicts a much smaller protein that migrates aberrantly on gels [61]. The role of the PM-Scl complex in the cell is unknown, but it may be involved in pre-ribosomal formation [59].

Anti-Ku has also been associated with scleroderma-polymyositis overlap. It was first described in Japan [63], where it is found more commonly among patients with this overlap syndrome than is anti-PM-Scl [53], the latter being found predominantly in Caucasian patients. Anti-Ku antibody, however, is also common in SLE without myositis, particularly in patients with anti-Sm without anti-U1RNP [64], and cannot be considered a myositis-specific antibody. Anti-Ku is unusual among autoantibodies because of its relative species specificity, reacting much better with human antigen than that of other species. In most cases it reacts with conforma-

tional epitopes [65], and the areas of the protein carrying several of the predominant epitopes have been shown to be subject to evolutionary change by sequence analysis [66]. Despite being originally described as a precipitin, most sera with anti-Ku do not show precipitating antibodies in Ouchterlony immunodiffusion or counter-immunoelectrophoresis against calf thymus extracts [64]. This may relate to its species specificity. The Ku antigen is a complex of proteins of 70 and 80–86 kD that binds to free ends of DNA, without apparent regard for the DNA sequence [67]. The role has not been determined, although it has been suggested that it may be involved in DNA repair. Most anti-Ku patient sera react with both proteins of Ku antigen in immunoblot.

Anti-U1RNP (antibody to the U1 small nuclear ribonucleoprotein) is common in patients with overlap syndromes involving myositis, particularly those including systemic lupus erythematosus as in mixed connective tissue disease, but also in patients with scleroderma-polymyositis overlap. Antibodies to the 68–70-kD protein have been associated with myositis in some studies [68,69]. This protein has been found to share short antigenic sequences with a murine retroviral gag protein [43] and an influenza B virus protein [70], suggesting that it may become antigenic through molecular mimicry. A much smaller percentage of patients has antibodies that react with U2RNP-specific proteins [71]. Their sera usually have antibodies to the B″ protein, and often also the A′ protein. Most sera with these antibodies also react with U1RNP, often through a cross-reaction of the B″-U2RNP and A-U1RNP proteins, although antibodies to other U1RNP proteins are also usually seen. The most common clinical picture associated with anti-U2RNP has been scleroderma-polymyositis overlap syndrome.

ANTI–Mi-2

Only one MSA, anti–Mi-2, has been specifically associated with DM as opposed to PM [72]. Over 95% of patients with anti–Mi-2 have had the DM rash [73]. This antibody is very strongly myositis-specific, being found in only one patient without myositis, who had features of the DM rash. In most patients with the antibody, the rash is florid and a prominent part of their disease, although it may also be subtle or overlooked at first. This myositis is usually more responsive and easier to treat than that associated with anti-synthetases [16], although it can be very severe. Generally, the features of the anti-synthetase syndrome have not been more frequent in patients with anti–Mi-2 than in others with myositis. Anti–Mi-2 may occur in juvenile DM, suggesting that at least some cases of juvenile DM are similar to adult DM. This is in contrast to anti–Jo-1, which, although more common than anti–Mi-2 overall, has not been seen in juvenile DM. This further demonstrates the clinical significance of the subgroups defined by the MSA.

Anti–Mi-2 may be detected by immunodiffusion and immunoprecipitation, but reactivity seems to be limited to conformational epitopes, because immunoblotting has been negative with all sera tested. The Mi-2 antigen, present in the cell nucleus, appears to be a complex of proteins, the most prominent of which is 220–240 kD, with additional components of 30, 63, 65, 75, 150 kD, and possibly others [73]. No nucleic acid is known to be associated with the antigen. Nothing is known about the cellular role of the Mi-2 antigen.

OTHER MSA

Unlike the MSA discussed above, each of which is found in a limited number of patients, usually representing a clinically recognizable subgroup, the anti–56-kD antibody has been reported to occur in all groups of myositis patients, including both DM and PM, and both adults and children [17]. Its titers tend to vary with disease activity. It was found in 85% of 52 myositis patients, but in none of 11 patients with other muscle diseases. However, it is not entirely myositis-specific, because low levels of the antibody have been found in up to 10% of patients with SLE or other conditions. The antibody is detected by immunoblot as a 56-kD protein of ribonucleoprotein particles isolated from Syrian hamster cell nuclei [74]. Its relation to the other MSA is unclear.

Also reported to occur in myositis are antibodies to muscle-specific proteins. Although many studies have failed to associate antibodies to muscle proteins with myositis, a few have reported such antibodies [75,76]. Wada et al reported antibodies to myosin in 90% of myositis patients, without regard to clinical subgroup, that correlated with disease activity [75]. As with anti-56 kD, these antibodies were also not completely specific for myositis, being found in other muscle diseases, but they were much more common and in higher titer in PM/DM. The lack of disease or subgroup specificity raises the possibility that they are secondary to muscle damage, which is much more likely with muscle-specific antibodies than with MSA.

SIGNIFICANCE OF THE MSA

The MSA are clearly important in understanding myositis because of their disease and subgroup specificity. An understanding of the origin of these antibodies may provide insight into the cause and pathogenesis of PM/DM. Production of these antibodies is influenced by the major histocompatibility complex. Anti–Jo-1 is strongly associated with HLA DR3 in white patients [77], although this association is not seen in black patients. All anti-synthetases, antibodies to translation-related proteins, and anti-SRP have been associated with HLA DRw52, in both black and white patients [16,77]. This has been proposed as the important association. Anti–PM-Scl is also very strongly associated with HLA DR3 [78], whereas anti–Mi-2 has been associated with HLA DR7 [16].

An unidentified factor working in the genetically susceptible individual appears to be important in the generation of the MSA, which may differ with different antibodies. As noted above, there is much speculation that this factor is a virus that may be responsible for causing the myositis. The production of the MSA may be one mechanism by which the tissue damage develops, or the MSA may be an epiphenomenon of a viral infection that may be responsible for induction of myositis through other mechanisms. There is no direct evidence that the antibodies are pathogenic, and the absence of antibody deposition in DM skin lesions or PM muscle speaks against their role. Furthermore, it is difficult conceptually to understand how these intracellular antigens can be a primary target of attack.

However, certain considerations indicate that a possible role for these antibodies warrants further study. First, there is a general correlation of anti–Jo-1 titer and disease activity. This was found in at least two studies [30,41], although not all studies agree. Improvement and especially complete remission of disease seem to be associated consistently with a fall in titer and occasionally with the disappearance of the antibody [41], and the new appearance of antibody was followed by the development of the disease [35]. A correlation of antibody titer has been found with disease activity index and with creatine kinase level [41]. Anti–Jo-1 is seldom found in the absence of myositis, and then usually in patients with ILD. Anti–PL-7 has also been correlated with disease activity [79].

There is also a possibility that under some circumstances the intracellular antigens of the MSA are expressed on the surface of muscle or other cells, which might explain how either cell-mediated or humoral attack directed at the antigens could contribute to tissue damage. Although true MSA have not been demonstrated on cell surfaces, other antigens, including Ro/SSA [80], ribosomal P_o [81], and 70-kD Ku [82], have been found to be expressed on the cell surface membrane under some conditions. Such expression could conceivably be related to cell insults such as viral infection. An additional possibility is that autoantibodies enter cells under some circumstances, but the likelihood of such a process occurring to a significant degree seems more difficult to support.

FUTURE STUDIES

The future study of humoral immunity in myositis will pursue an understanding of 1) the origin of the autoantibodies and their role in the various manifestations of PM/DM, and 2) the mechanisms for small vessel damage and local complement activation in DM. Further study of the autoantibodies and their precise epitope patterns will be facilitated by the availability of cloned antigens. As tests for

the antibodies become more widely available, their value in diagnosis and patient management will be clarified. An understanding of the MSA will be important not only in PM/DM but may bear on autoantibodies in other autoimmune disease.

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